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Formation of C(sp^2)–S Bond Through Decarboxylation of α-Oxocarboxylic Acids with Disulfides or Thiophenols

Guangwei Rong[a], Jincheng Mao,*[a,b]Defu Liu[a], Hong Yan[a], Yang Zheng[a], and Jie Chen[a]

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Copper-catalyzed decarboxylative coupling between α-oxocarboxylic acids and diphenyl disulfides or thiophenols was presented, which provided an effective and direct approach for the preparation of such useful thioesters through C(sp^2)-S bond formations.

In the recent years, transition-metal-catalyzed decarboxylative cross-coupling has attracted great attention on the formation of carbon-carbon and carbon-heteroatom bonds, since acids and their derivatives are usually stable, low-cost and commercially available substrates.[1] Different from the traditional cross-coupling methods, which need pre-activated partners such as organometallic reagent and thus generated toxic metal wastes, transition-metal-catalyzed decarboxylative cross-coupling reactions generally prefer to employ catalytic amount of metal catalysts such as palladium, copper, iron salts and et al.[2] Among these atom economical and green protocols, arylcarboxylic acids or arylcarboxylates were often used as aryl sources.[3] Excellent works on decarboxylative coupling reactions using benzoic acids and cinnamic acids have been extensively studied in the past several years.[4] However, the area of decarboxylative reactions of benzoylformic acids has not been fully explored.[5] It was firstly reported by Elena Vismara and his coworkers about silver-catalyzed decarboxylative acylation reaction in 1991.[5a] Then, the related decarboxylative couplings were developed by different groups as shown in Scheme 1. For example, Goossen and co-workers have reported Cu/Pd-catalyzed decarboxylation of α-oxocarboxylates and aryl bromides.[5b,5c] Ge and Li showed an example of Pd(II)-catalyzed decarboxylative cross-coupling of potassium aryltrifluoroborates with α-oxocarboxylic acids.[5d] After that, many researches focused on the combination of decarboxylation and C–H activation or functionalization, since this is a more straightforward way.[5e-5i] In 2009, Ge and co-workers just described a Pd-Catalyzed decarboxylative *ortho*-acylation of acetanilides with α-oxocarboxylic acids.[5j] From then on, a series of works on C-C formation *via* directed *ortho*-direction from decarboxylation of α-oxocarboxylic acids came out.[5k-5r] Recently, Duan and co-workers disclosed silver-catalyzed decarboxylative acylarylation of acrylamides with α-oxocarboxylic acids in aqueous media.[5s] Based on the above examples, it can be seen that C-C formation reactions were performed smoothly *via* decarboxylation of α-oxocarboxylic acids. However, researches on carbon-heteroatom formation were less reported till now. Thus, in this paper, we will present our results on copper-catalyzed decarboxylation of α-oxocarboxylic acids with disulfides or thiophenols to prepare the useful thioesters through C(sp^2)-S bond formations.

[a]*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China.*
[b]*State Key Laboratory of Oil and Gas Reservoir Geology and Exploitation, Southwest Petroleum University, Chengdu 610500, P. R. China*
E-mail: jcmao@suda.edu.cn
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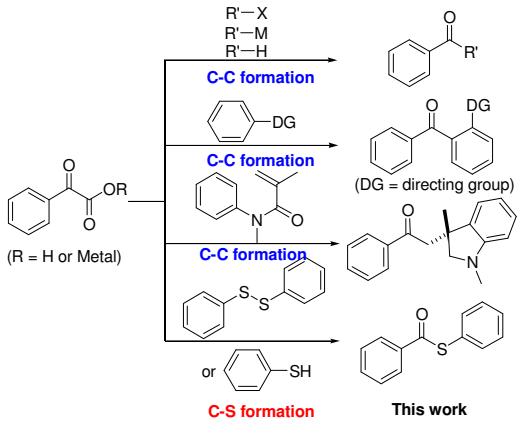
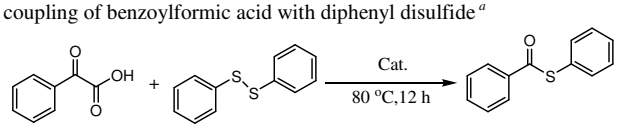


Scheme 1. Decarboxylation of benzoylformic acid

As we know that thioesters play pivotal roles in biology as they are important structure units in various natural compounds. Besides, they also serves as essential synthetic intermediates for a range of acyl transfer reactions.[6] Traditionally, thioester was prepared from benzoyl chloride and thiophenol. Considering the hygroscopicity and instability of benzoyl chloride, more practical approaches were developed using benzaldehydes as starting materials in recent years.[7] Unlike previous reported protocols, thioesterification also can also be achieved through α-oxocarboxylic acids and disulfides with our method, which provides an alternative way to access thioesters.

In our initial attempt, benzoylformic acid and diphenyl disulfide were chosen as model substrates to screen the optimal reaction conditions and the results are shown in table 1. Using 20 mol% of cupric acetate as catalyst, stoichiometric $(NH_4)_2S_2O_8$ as oxidant and acetonitrile as solvent, desired product was achieved in the yield of 28% (Table 1, entry 1). Controlled experiments confirmed that the reaction can not occur without catalyst or oxidant. The reaction also can not proceed smoothly using the traditional system of Ag(I)/$(NH_4)_2S_2O_8$. Then, we screened various copper catalysts and CuO showed best catalytic efficiency, affording the product **3a** in 33% yield (Table 1, entry 7). Different oxidant were tested and $(NH_4)_2S_2O_8$ was proved to be one of the best (Table 1, entires 12-14). Most solvents were not suitable to this reaction during the process of optimization, only DMSO showed good effect and 65% **3a** was achieved (Table 1, entry 12). Given that mixed solvent was widely adopted in decarboxylative reactions, we next tried various co-solvent such as DMSO/CH_3CN and DMSO/dioxane in a ratio of 10:1. We were pleased to find that **3a** was obtained in 74% yield when DMSO/H_2O as solvent (Table 1, entry 15). Through the adjustment of the proportion of solvent, we found that the optimum solvent ratio of DMSO/H_2O was 5:1 and the yield was increased to 83% (Table 1, entry 18). The amount of **2a** was also tested (Table 1, entries 19-20) and 2 equivalents proved to be the

Table 1. Optimization of reaction conditions for the decarboxylative coupling of benzoylformic acid with diphenyl disulfide [a]



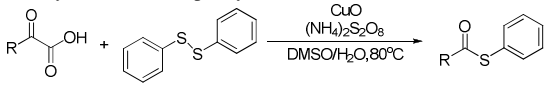
Entry	Cat.	Oxidant	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$	$(NH_4)_2S_2O_8$	CH_3CN	28
2	Cu	$(NH_4)_2S_2O_8$	CH_3CN	29
3	CuI	$(NH_4)_2S_2O_8$	CH_3CN	Trace
4	$CuCl_2$	$(NH_4)_2S_2O_8$	CH_3CN	<10
5	$CuSO_4$	$(NH_4)_2S_2O_8$	CH_3CN	31
6	CuF_2	$(NH_4)_2S_2O_8$	CH_3CN	31
7	CuO	$(NH_4)_2S_2O_8$	CH_3CN	33
8	CuO	$(NH_4)_2S_2O_8$	Dioxane	NR
9	CuO	$(NH_4)_2S_2O_8$	Toluene	NR
10	CuO	$(NH_4)_2S_2O_8$	DCE	NR
11	CuO	$(NH_4)_2S_2O_8$	DMF	NR
12	CuO	$(NH_4)_2S_2O_8$	DMSO	65
13	CuO	$K_2S_2O_8$	DMSO	50
14	CuO	$Na_2S_2O_8$	DMSO	45
15	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=20/1	74
16	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=10/1	78
17	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=7/1	82
18	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=5/1	83
19[c]	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=5/1	72
20[d]	CuO	$(NH_4)_2S_2O_8$	DMSO/H_2O=5/1	83

[a] Catalytic conditions: Benzoylformic acid (0.3 mmol), diphenyl disulfide (0.3 mmol), cat. (20 mol%), oxidant (0.6 mmol), solvent (2 mL), 80 °C, 12 h, air; [b]Isolated yield; [c] **2a** (0.15 mmol); [d] **2a** (0.45 mmol).

best. *S*-phenyl benzenesulfonothioate was detected after the reaction which can explain why disulfide should be excessive.

With optimized reaction conditions in hand, we next investigated the scope of different α-oxocarboxylic acids. As shown in table 2, various substituted α-oxocarboxylic acids, including methyl, halogen and methoxy groups, were tolerable under the optimal conditions. Generally, α-oxocarboxylic acids bearing an electron-donating group gave the products in higher yields than those with electron-withdrawing analogues. Methy-substituted from **3b** to **3d** all proceeded well and gave in good yields (Table 2, entries 2-4).

Table 2. Copper-catalyzed decarboxylative coupling between various α-oxocarboxylic acids and diphenyl disulfide (**2a**) [a]



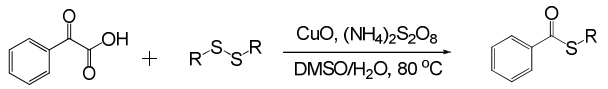
1 **2a** **3**

Entry	R	Product	Yield [b] [%]
1	C_6H_5	**3a**	83
2	4-MeC_6H_4	**3b**	84
3	3-MeC_6H_4	**3c**	86
4	2-MeC_6H_4	**3d**	82
5	4-FC_6H_4	**3e**	81
6	4-ClC_6H_4	**3f**	60
7	4-BrC_6H_4	**3g**	51
8	3-BrC_6H_4	**3h**	34
9	2-BrC_6H_4	**3i**	54
10	4-$MeOC_6H_4$	**3j**	86
11	2-FC_6H_4	**3k**	60
12	2-ClC_6H_4	**3l**	53
13	2-thienyl	**3m**	79
14	2-naphtyl	**3n**	82
15	Methyl	**3o**	56

[a] Catalytic conditions: Benzoylformic acid (0.3 mmol), diphenyl disulfide (0.3 mmol), $(NH_4)_2S_2O_8$ (0.6 mmol), CuO (20 mol%), $(NH_4)_2S_2O_8$ (0.6 mmol), DMSO/water (5/1) (2 mL), 80 °C, 12 h, air. [b]Isolated yield.

The yields of *p*-halogen substrates were decreased from **3e** to **3g** (Table 2, entries 5-7). It is the same situation for *o*-halogen substrates **3k** and **3l** (Table 2, entries 11-12). *Meta*-bromine benzoylformic acid afforded product (Table 2, entry 8) in lower yield than *ortho* and *para*-bromine acids. We guess that the poor conjugated effect perhaps caused the difference when bromine located in the *meta* position. For heterocyclic and fused ring substrates, **3m** and **3n** can be achieved in good yields of 79% and 82%, respectively. Furthermore, aliphatic α-oxocarboxylic acid was also suitable substrate in this reaction, giving a moderate yield (**3o**) (Table 2, entry 15).

Table 3. Copper-catalzyed decarboxylation of benzoylformic acid and various disulfides [a]



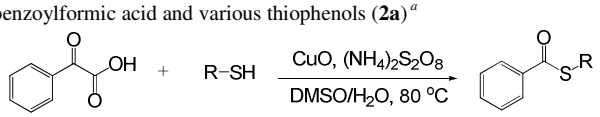
1a **2** **3**

Entry	R	Product	Yield [b] [%]
1	4-MeC_6H_4	**3p**	80
2	4-$MeOC_6H_4$	**3q**	86
3	4-$NO_2C_6H_4$	**-**	NR
4	Benzyl	**3r**	65
5	n-Propyl	**3s**	52

[a] Catalytic conditions: Benzoylformic acid (0.3 mmol), disulfide (0.3 mmol), CuO (20 mol%), $(NH_4)_2S_2O_8$ (0.6 mmol), DMSO/water (5/1) (2 mL), 80 °C, 12 h, air. [b]Isolated yield.

As shown in Table 3, we then applied the optimal reaction conditions to decarboxylations of benzoylformic acid with various disulfides. Aromatic disulfides can afford the desired esters in good yields. Disulfide bearing strong electron donating group such as methoxy was converted into the corresponding thioester **3q** in 86% yield (Table 3, entry 2). However, the reaction was almost inhibited when *p*-nitro substituted disulfide was chosen as the substrate (Table 3, entry 3). It is pleased to find that aliphatic disulfides are good substrates, giving moderate yields (**3r**, **3s**) (Table 3, entries 4-5).

Table 4. Copper-catalyzed decarboxylative coupling between benzoylformic acid and various thiophenols (**2a**) [a]



1a **4** **3**

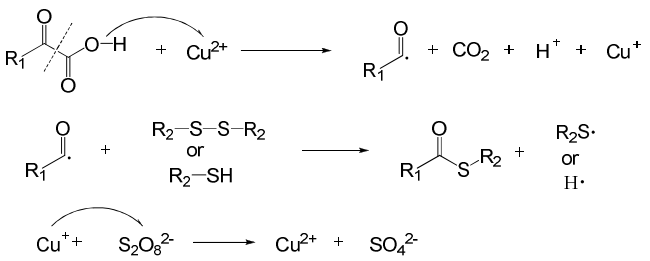
Entry	R	Product	Yield [b] [%]
1	C_6H_5	**3a**	74
2	2-MeC_6H_4	**3t**	73
3	2,6-$Me_2C_6H_3$	**3u**	75
4	2-ClC_6H_4	**3v**	66
5	2-FC_6H_4	**3w**	72
6	2-thienyl	**3x**	45

[a] Catalytic conditions: Benzoylformic acid (0.3 mmol), thiophenol (0.6 mmol), CuO (20 mol%), $(NH_4)_2S_2O_8$ (0.6 mmol), DMSO/water (5/1) (2 mL), 80 °C, 12 h, air. [b]Isolated yield.

As we know that thiols have disadvantages of operating inconvenience and unpleasant odour in comparison to disulfides. Considering the similarity of their structure, we further extended the reaction to a series of thiols. Various substituted thiols all gave the corresponding products in moderate to good yields as shown in Table 4. It is obvious to find that the desired thiols show less efficiency in thioesterification compared to disulfides. Anyway, it provides alternative choice of substrates as thiols are more cheaper

and commercially available. It was found that disulfide was dectected after reaction, which indicated that the reaction may go through a process that thiophenol was converted into the corresponding disulfide before reacting with benzoylformic acid.

Based on previous reports about decarboxylations[5a,7], we proposed a possible mechanism as shown in Scheme 3. Firstly benzoylformic acid generates benzoyl radical in the presence of copper(II) catalyst. The radical then further reacts with disulfide or thiophenol to give the thioester. The copper(I) ion will be next oxdized to copper(II) by ammonium persulfate and back into the reaction.



Scheme 3. Plausible mechanism

In conclusion, we have presented an efficient method to prepare thioesters involving $C(sp^2)$–S bonds formation through decarboxylative coupling of α-oxocarboxylic acids and disulfides or thiophenols. Furthermore, the thioesters prepared by our method will show valuable properties such as nucleophile acceptors, which means they can serve as one of the most important intermediates in organic synthesis.[8] Further application of the reaction will be the key point of our future work.

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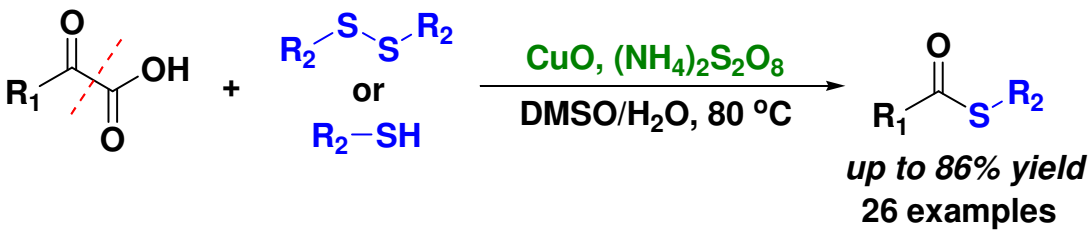
Graphical abstract



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