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Photo-oxidative Cross-Dehydrogenative Coupling-Type Reaction of Thiophenes with α-Position of Carbonyls Using a Catalytic Amount of Molecular Iodine

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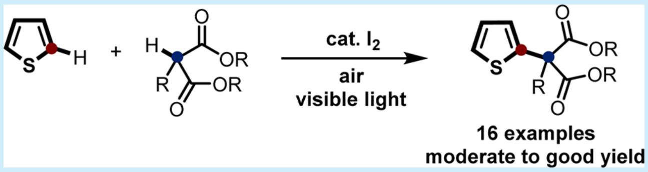
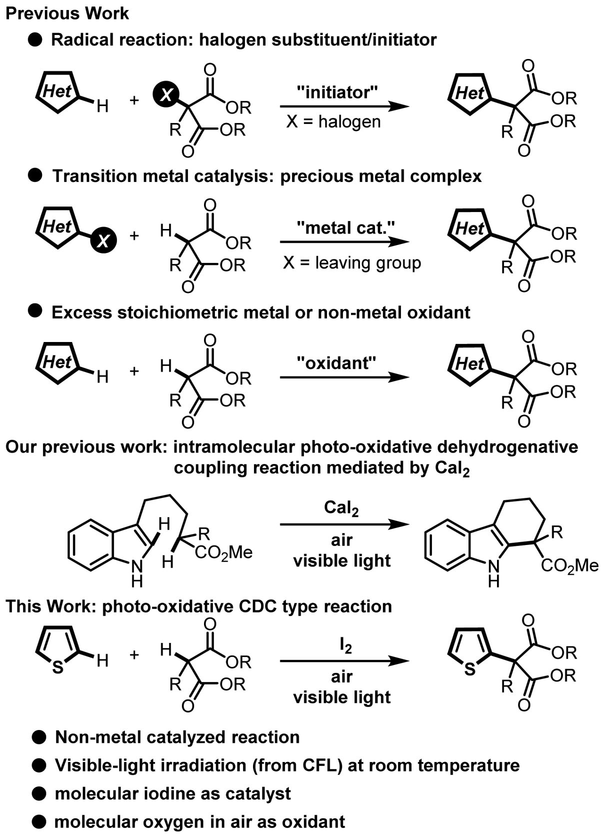
Supporting Information

ABSTRACT: A metal-free photo-oxidative intermolecular C−H/C−H coupling reaction of thiophenes is demonstrated with carbonyls using a catalytic amount of molecular iodine. In this system, molecular oxygen in the air acted as a terminal oxidant to regenerate molecular iodine. A mechanistic study was also performed.



The introduction of heteroarenes at the α-position of carbonyls is one of the fundamental research topics in organic synthesis, as the molecules that contain such fragments are ubiquitously found in naturally occurring molecules and pharmaceuticals and exhibit diverse biological and pharmacological activities.[1] Owing to diverse pharmaceutical applications, methodologies for construction of a C−C bond at the α-position of carbonyls have been extensively investigated (Scheme 1).[2] While the reaction with a C-centered radical, which leads to the corresponding carbon−carbon bond-forming product, is one of the most well-established reactions, the generation of radical species from α-halo carbonyls is mediated by a radical initiator or a mediator such as AIBN, tin, or trialkylborane.[3] However, many radical initiation systems require harsh reaction conditions and functional group tolerance and also produce byproducts. Therefore, more atom-economical reactions that use photoredox catalysis to chemoselectively reduce a suitable carbon−halogen bond under mild conditions have been studied.[4] Although numerous photocatalysts based on Ru or Ir have been investigated during the past decades, these complexes are expensive and potentially toxic.[5] The coupling reaction of halogenated heteroarenes with carbonyls is a suitable method for forming a C−C bond.[6] This methodology shows good functional group tolerance and generally a better yield compared with the above reaction. However, the method requires a precious transition-metal complex. Recently, a stoichiometric heavy- or transition-metal-catalyzed intermolecular C−H/C−H coupling reaction between carbonyls and heteroarenes has been reported.[7] Furthermore, a Mn-catalyzed cross-dehydrogenative coupling reaction of heteroarenes with carbonyls using cheap $NaIO_4$ as co-oxidant was reported by Yamaguchi and co-workers.[8] However, a catalytic and aerobic oxidation methodology has not been achieved for the CDC coupling of heteroarenes with carbonyls.

Scheme 1. Summary of C−C Bond-Forming Reaction at the α-Position of Carbonyls with Heteroarenes



We have studied aerobic photo-oxidative reactions mediated by a halogen source.[9] During the course of this study, we have observed a rare-metal-free catalytic photoaerobic intramolecular dehydrogenative C−C bond-forming reaction from two C−H bonds of indole with malonate.[10] This system proceeded at room temperature under visible light irradiation from CFL with

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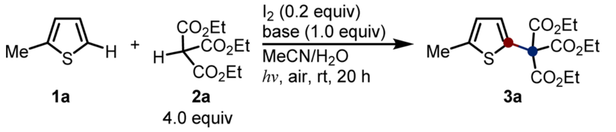
aerobic oxygen as a terminal oxidant. On the basis of this pioneering result, a metal-free intermolecular catalytic cyclization reaction should be achievable using heteroarenes with carbonyls. Herein, we describe the development of a practical method for an aerobic photo-oxidative intermolecular C−H/C−H coupling of carbonyls and thiophenes using a catalytic amount of molecular iodine (Scheme 1).

We first investigated the C−H/C−H coupling reaction of **1a** with **2a** in the presence of a catalytic amount of molecular iodine with visible light irradiation at room temperature to achieve a dehydrogenative-type coupling reaction leading to **3a** (Table 1 and Table S1). First, the solvent was considered while maintaining a concentration of 0.3 M (entries 1−6). The use of acetonitrile as a solvent led to C−C bond formation, resulting in **3a** as the main product although with incomplete conversion of thiophene **1a** (entry 6). Conducting the reaction in a mixed solvent of acetonitrile and water provided the desired product **2a** in higher yield (entry 7). We then investigated base screening with various salts (entries 8−14). Ultimately, a combination of catalytic molecular iodine and K_3PO_4 (1.0 equiv) delivered the product **3a** in 72% NMR yield (entry 14). The yield of product was increased to 80% (77% isolated) when the reaction was conducted at a lower concentration (entry 16). Finally, efforts to increase the yield revealed that a small excess of K_3PO_4 over the stoichiometric level was essential to yield the product (83% isolated yield, entry 17). All reactions gave the corresponding hydroxylated malonate **2a-OH** in moderate yield.

Table 1. Optimization Study of C−H/C−H Coupling of 2-Methylthiophene 1a with Triester 2a[a]

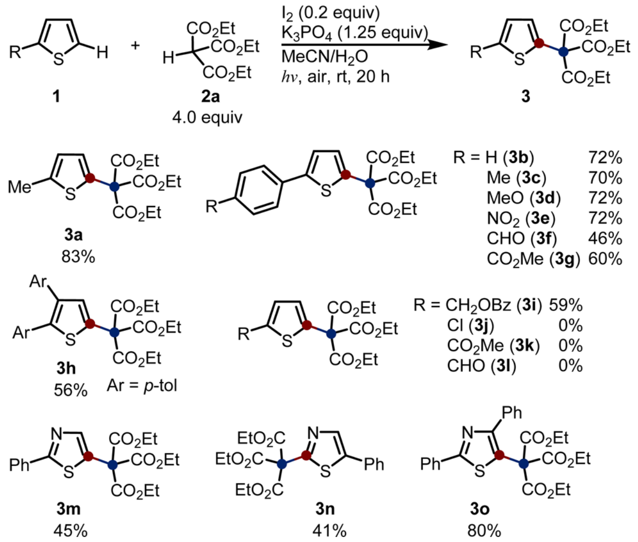


entry	base	solvent (mL)	yield[b,c] (%)
1[d]	$Ca(OH)_2$	$CHCl_3$ (1)	trace
2[d]	$Ca(OH)_2$	DMAc (1)	trace
3[d]	$Ca(OH)_2$	DMSO (1)	trace
4[d]	$Ca(OH)_2$	MeOH (1)	20
5[d]	$Ca(OH)_2$	EtOAc (1)	38
6[d]	$Ca(OH)_2$	MeCN (1)	52
7	$Ca(OH)_2$	$MeCN/H_2O$ (2/0.2)	67
8	$CaCO_3$	$MeCN/H_2O$ (2/0.2)	58
9[e]		$MeCN/H_2O$ (2/0.2)	58
10	$Mg(OH)_2$	$MeCN/H_2O$ (2/0.2)	63
11	CsOH	$MeCN/H_2O$ (2/0.2)	72
12	Cs_2CO_3	$MeCN/H_2O$ (2/0.2)	72
13	K_2HPO_4	$MeCN/H_2O$ (2/0.2)	60
14	K_3PO_4	$MeCN/H_2O$ (2/0.2)	72
15	K_3PO_4	$MeCN/H_2O$ (3/0.3)	72
16	K_3PO_4	$MeCN/H_2O$ (4/0.4)	80 (77)
17[f]	**K_3PO_4**	**$MeCN/H_2O$ (4/0.4)**	**(83)**

[a] Conditions: The mixture of 2-methylthiophene **1a** (0.3 mmol), **2a** (4.0 equiv), I_2 (0.2 equiv), and base (1.0 equiv) in solvent and water was stirred for 20 h in an aerobic atmosphere at ambient temperature and irradiated with four 22 W compact fluorescent lamps. [b] Yields were determined by ^1H NMR analysis of the crude reaction mixture. [c] Numbers in parentheses refer to isolated yield. [d] 2.0 equiv of **2a** was employed. [e] 0.2 equiv of CaI_2 was employed instead of I_2. [f] 1.25 equiv of K_3PO_4 was employed.

With the optimal conditions in hand, we investigated the scope of C−H/C−H coupling of tris(ethoxycarbonyl)methane (**2a**) with thiophenes (**1**) (Scheme 2). When 2-phenylthiophene (**1b**) was used, the coupling proceeded well to give the corresponding product **3b** in 72% yield. Substituents at the aryl group on the thiophene ring did not affect the reactivity of this C−C bond-forming reaction. A 2,3-diarylated thiophene also reacted smoothly to give the corresponding product **3h** in moderate yield. To our delight, benzoyl-protected 2-thiophenemethanol (**1i**) also reacted without undesired oxidation reactions at the benzylic position. In contrast to these results, electron-poor thiophenes, such as 2-chloro (**1j**), 2-methoxycarbonyl (**1k**), and 2-formyl (**1l**), did not react under the present conditions. Moreover, 2-phenyl (**1m**), 5-phenyl (**1n**), and 2,5-diphenylthiazole (**1o**) were also compatible under the optimal conditions and gave the monocoupling product in moderate to good yields.

Scheme 2. Substrate Scope Exploration Using Thiophene and Thiazole Derivatives 1 with Triester 2a[a,b]



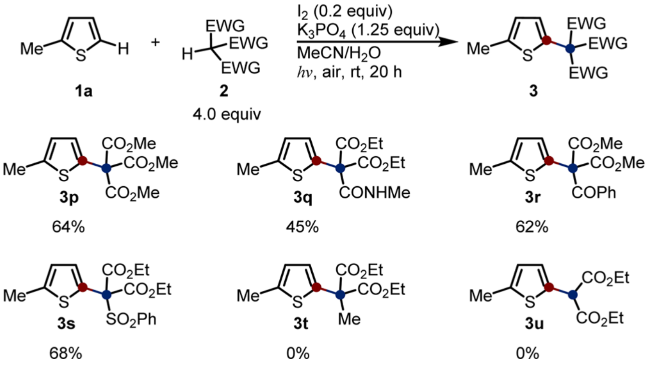
[a] Conditions: The mixture of **1** (0.3 mmol), **2a** (4.0 equiv), I_2 (0.2 equiv), and K_3PO_4 (1.25 equiv) in MeCN (4 mL) and water (0.4 mL) was stirred for 20 h in an aerobic atmosphere at an ambient temperature and irradiated with four 22 W compact fluorescent lamps. [b] Isolated yield.

After the functional group tolerance of heteroarenes was demonstrated, the diversity of carbonyls was further investigated under optimal conditions (Scheme 3).

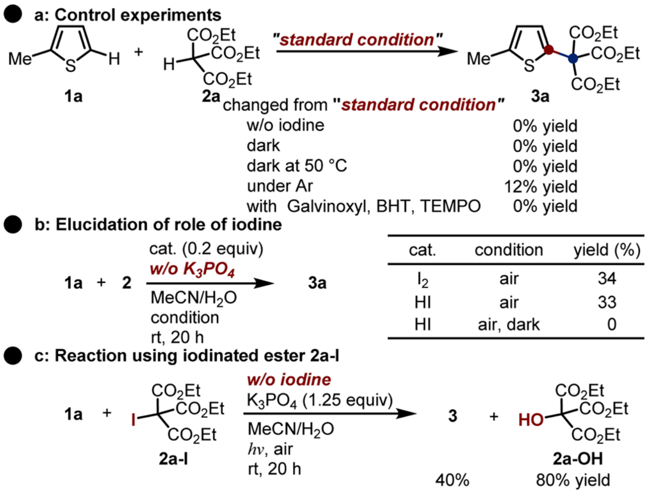
Overall, moderate to good yields of **3** were obtained, and various substituents on the carbonyls, e.g., amide, ketone, and sulfonyl, showed little effect on the efficiency of the reaction. The ^1H NMR analysis of the crude reaction mixture of **3p** showed a large amount of the corresponding hydroxylated trimethylcarboxylate. This indicated that the ethyl ester moiety could suppress the oxidation at the α-position of carbonyl. Unfortunately, diethyl methylmalonate and diethyl malonate did not react with thiophene to give the corresponding products **3t** and **3u.**[11]

We conducted detailed control experiments to elucidate the role of molecular iodine in this CDC-type reaction (Scheme 4, eq a). Under the optimized reaction conditions in the absence of molecular iodine, **1a** is not converted into the desired product. The reaction in the dark did not give a product, even

Scheme 3. Substrate Scope Exploration Using 1a with Carbonyls 2



Scheme 4. Mechanistic Studies



cat.	condition	yield (%)
I_2	air	34
HI	air	33
HI	air, dark	0

when heated. This coupling reaction under an argon atmosphere gave 12% of product, and the results demonstrated that only a trace amount of **1a** was coupled with **2a** in the absence of molecular oxygen. Moreover, radical-trapping reagents (galvinoxyl, BHT, and TEMPO) completely suppressed the reaction. These experiments revealed that I_2, visible light, and molecular oxygen are indispensable in this transformation, and the reaction could proceed through the radical intermediate. To gain an insight into the role of iodine, several experiments were carried out (eq b). The yield of **3a** was decreased to 34% when the reaction was performed without K_3PO_4 in air. And the reaction using hydroiodic acid as catalyst also gave the product in 33% yield. However, the reaction using HI in the dark did not furnish the product. Based on these results, we assumed that molecular iodine could be (re)-generated from iodide in the presence of oxygen and act as a catalyst. Finally, to clarify the intermediate of this reaction, iodinated ester **2a-I** was used as a coupling partner (eq c). As a result, the reaction gave the desired product in 40% yield and hydroxylated ester **2a-OH**.[12] The result indicated that **2a-I** might be the intermediate of the reaction and could form a C-centered radical via C−I homolytic cleavage mediated by visible light.[10]

Based on the experimental data, a plausible mechanism is outlined in Figure 1. Initially, the mixture of ester and molecular iodine generated a plausible iodinated intermediate **2-I**. Visible-light irradiation from CFL caused homolytic cleavage of the C−I bond, which generated the *C*−centered radical species **I**. Addition of **I** to thiophenes and iodination of the generated radical gave intermediate **II**. Finally, aromatization of **II** furnished product **3**.

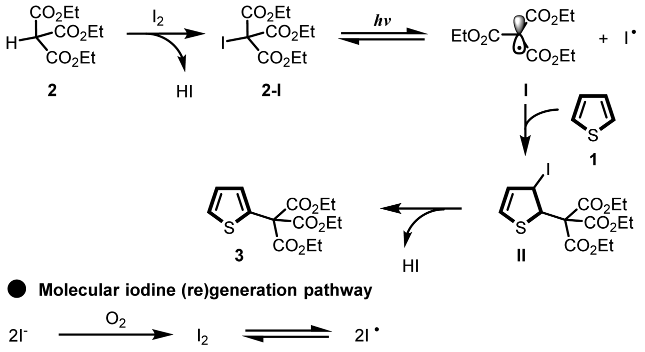


Figure 1. Plausible reaction mechanism.

In conclusion, a novel and concise route to gain *α*-heteroarylated carbonyls via an aerobic photo-oxidative C−H/C−H coupling reaction of heteroarenes with carbonyls, mediated by molecular iodine has been developed. This reaction proceeds through activation of cheap and abundant molecular iodine and the formation of C−C bonds. In contrast to traditional methods leading to similar products, the advantages of this methodology are mild reaction conditions, operational simplicity, and an inexpensive and abundant molecular iodine catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00428.

Experimental and characterization data; ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(11) The reaction using diethtyl methylmalonate only gave the corresponding hydroxide. This indicated that generated *C*-centered radical was preferred to react with oxygen. However, the reaction using diethyl malonate only recovered the unreacted diethyl malonate. Thus, the iodination of diethyl malonate did not occur under the conditions.

(12) Formation of **2a-OH** proceeded through the reaction of **I** with triplet oxygen. See: Tada, N.; Shomura, M.; Nakayama, H.; Miura, T.; Itoh, A. *Synlett* **2010**, *2010*, 1979. See also ref 9a.