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Iodine-Catalyzed Radical Oxidative Annulation for the Construction of Dihydrofurans and Indolizines

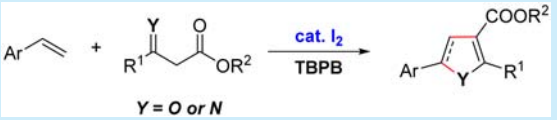
Shan Tang,[†,§] Kun Liu,[†,§] Yue Long,[†] Xinlong Gao,[†] Meng Gao,[‡] and Aiwen Lei*[,†,‡]

[†]College of Chemistry and Molecular Sciences, The Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, People's Republic of China

[‡]National Research Center for Carbohydrate Synthesis, Jiangxi Normal University, Nanchang 330022, People's Republic of China

Supporting Information

ABSTRACT: Through iodine catalysis, the direct oxidative coupling/annulation of β-keto esters or 2-pyridinyl-β-esters with alkenes was achieved. This reaction procedure provides a simple and selective way for the synthesis of dihydrofurans and indolizines in one step.

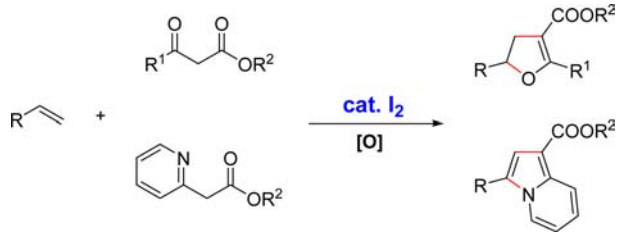


Heterocycles are among the most important constituents in natural products, pharmaceuticals, and materials. Thus, continuous efforts have been devoted to their syntheses.[1] According to the requirements of atom-economical and sustainable chemistry, direct utilization of two different hydrocarbons as reagents to construct chemical bonds is an ideal approach in organic synthesis.[2] From this viewpoint, developing efficient and practical methods for the syntheses of heterocyclic compounds from two hydrocarbons is very important.

Oxidative coupling/annulation of 1,3-dicarbonyl compounds with alkenes has been well-known as an effective approach for the synthesis of dihydrofurans.[3] However, in most cases, these reactions require the use of a large excess of transition metal oxidants such as Mn(III), Cu(II), and Ce(IV) salts.[4] Utilization of the excess transition metal salts as oxidants makes them difficult to operate and non-economical to scale up. These problems hinder the practical application of these transformations. In 2013, hypervalent iodine reagent iodobenzene diacetate was found to be able to promote the oxidative coupling/annulation of 1,3-cyclohexanedione with alkenes.[5] With a good capacity for electron transfer processes, iodine has recently been reported to serve as an alternative catalyst for transition metals in many reactions.[6] Thus, we wonder whether an iodine catalysis strategy can be developed to avoid the use of transition metals in the radical oxidative annulation of 1,3-dicarbonyl compounds with alkenes.

Actually, iodine catalysis has been widely applied in the direct oxidative α-C(sp^3)−H functionalization of carbonyl compounds. In the past few years, many C−O[7] and C−N[8] bond formation reactions of carbonyl compounds have been developed under iodine-catalyzed oxidative conditions. Among these transformations, nucleophilic substitution to the in situ generated α-C(sp^3)−I bond formation intermediates was the most widely accepted reaction pathway. Nucleophiles, such as acids and amines, were able to couple with this intermediate through iodine catalysis.[7,8] However, the nucleophilic substitution reaction strategy was unsuitable for unactivated hydrocarbon nucleophiles such as alkene. Therefore, a new iodine-catalyzed reaction pathway needs to be explored. With continuous interest in the α-functionalization of carbonyl compounds,[9] we herein communicate our progress in the iodine-catalyzed radical oxidative annulation of β-keto esters or 2-pyridinyl-β-esters with alkenes for synthesizing dihydrofurans and indolizines (Scheme 1).

Scheme 1. Radical Oxidative Annulation with β-Keto Esters and 2-Pyridinyl-β-esters



With considerable efforts, we found that the combination of I_2 and TBPB (*tert*-butyl peroxybenzoate) with NaOAc as additive could give a good result for the oxidative coupling/annulation of *p*-methylstyrene (**1a**) with methyl acetoacetate (**2a**) under mild conditions. Corresponding dihydrofuran was obtained in 77% isolated yield with good regioselectivity (Scheme 2, **3a**). Since good results were achieved, we first tried to explore the functional group tolerance for the synthesis of various dihydrofurans under the standard conditions. *para*-*tert*-Butylstyrene afforded the coupling product in 72% yield (Scheme 2, **3b**). Electron-rich *p*-methoxystyrene was suitable in this transformation (Scheme 2, **3c**). Halide substituents were tolerated in this transformation, and the reaction proceeded chemoselectively to afford the cyclization products (Scheme 2, **3d**−**3f**). Moreover, styrene with a reactive chloromethyl group at the para position was also able to furnish the desired product in a moderate yield (Scheme 2, **3g**). 2-Vinylnaphthalene and *ortho*-methylstyrene also showed good reactivity in the generation of the annulation product

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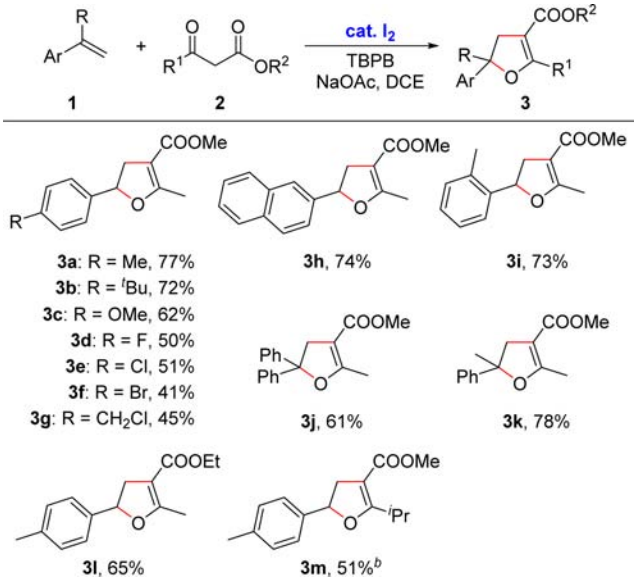
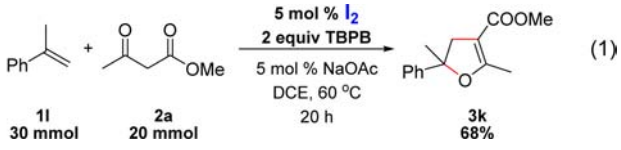
Scheme 2. Substrate Scope of the I_2-Catalyzed Oxidative Cross-Coupling/Annulation of β-Keto Esters with Alkenes[a]



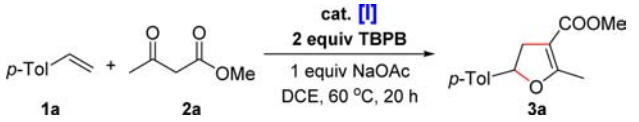
[a]Reaction conditions: **1** (0.75 mmol), **2** (0.50 mmol), I_2 (10 mol %), TBPB (1.0 mmol), NaOAc (0.50 mmol) in DCE (2.0 mL), 60 °C, 20 h. [b]TBPB (0.50 mmol) was used.

(Scheme 2, **3h** and **3i**). Unfortunately, strong electron-deficient styrenes such as 1-(trifluoromethyl)-4-vinylbenzene and 4-vinylbenzonitrile were unreactive in this transformation. Moreover, it should be mentioned that disubstituted terminal alkenes were also suitable in the reaction system. It was found that 1,1-diphenylethene and α-methylstyrene were both suitable in this transformation (Scheme 2, **3j** and **3k**). As for other types of β-keto esters, ethyl acetoacetate and iobutyrylacetic acid methyl ester were both applied and afforded the desired products in moderate yields (Scheme 2, **3l** and **3m**). To demonstrate the reaction efficiency of this iodine catalysis system, we tried to expand the reaction to a 20 mmol scale. In the case of **3k**, the loading of molecular iodine catalyst and base additive could be reduced to 5.0 mol %. A good reaction selectivity and yield could still be obtained (eq 1). Obviously, this is a great advantage of the iodine catalysis system over the $Mn(OAc)_3$-mediated processes according to the demand for atom-economical and sustainable chemistry.



To understand the role of iodine in this oxidative coupling/annulation process, we applied different kinds of iodine catalysts in the model reaction. To our surprise, a commonly used iodide catalyst, $^nBu_4NI$, was ineffective for the formation of the desired product (Table 1, entry 2). However, an iodine radical source, *N*-iodosuccinimide (NIS), showed a reactivity similar to that of molecular iodine (Table 1, entries 1 and 3). Iodobenzene was also tried, but no reaction took place (Table 1, entry 4). In the next step, control experiments were carried out to obtain further information. In the absence of iodine catalyst, no reaction could be observed (Table 1, entry 5).

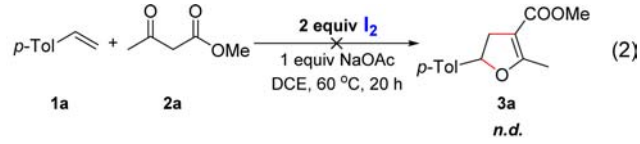
Table 1. Effect of Iodine Source[a]

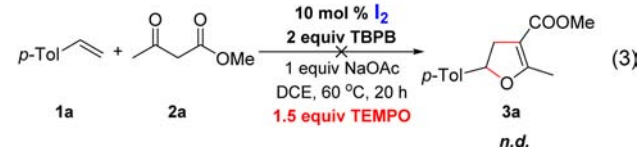


entry	iodine source	yield of **3a** (%)[b]
1	10 mol % of I_2	74
2	20 mol % of $^nBu_4NI$	trace
3	20 mol % of NIS	78
4	20 mol % of PhI	nr
5	none	nr

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.50 mmol), catalyst and TBPB (1.0 mmol), NaOAc (0.50 mmol) in DCE (2.0 mL), 60 °C, 20 h. [b]Yields are determined by GC analysis with biphenyl as the internal standard; nr = no reaction.

At the same time, no desired product could be obtained by using a stoichiometric amount of I_2 as the oxidant in the absence of peroxides (eq 2). These results indicated that the iodine





radical and hypervalent iodine species were both likely to be involved during the reaction system. At last, a radical-trapping experiment was carried out to confirm whether this reaction went through a radical reaction pathway. When a commonly used radical-trapping reagent, TEMPO, was added into the reaction system, no desired product could be observed for the oxidative coupling/annulation of **1a** with **2a** (eq 3).

Based on the results described above and in the previous reports,[4,10] we outlined a radical addition/cyclization mechanism (Scheme 3). It has been reported that I_2 could be oxidized by peroxides to generate I^+.[11] In the first step, β-keto ester could be oxidized by the in situ generated I^+ to generate an α-carbonyl carbon radical **I**. In the following step, radical addition of **I** to alkene would generate a benzylic radical **II**. Then, an intramolecular radical addition of **II** to the C=O bond would generate a five-membered hydrofuran ring. The radical intermediate **III** might either be oxidized by the in situ generated hypervalent species or go through a hydrogen abstraction process by a *tert*-butoxyl radical to furnish the desired dihydrofuran product. Since α-carbonyl carbon radicals are electrophilic radicals, radical addition of **I** to electron-rich alkenes is generally faster than to electron-deficient alkenes.[3] It might provide an explanation for the poor reactivity with electron-deficient styrenes in our transformation.

To further demonstrate the applicability of this iodine catalysis system, substrates with a structure similar to that of β-keto esters were explored under the standard conditions. 2-Pyridinyl-β-esters were found to be suitable in the oxidative cross-coupling/annulation with styrenes. With the use of a catalyst and oxidant combination of I_2 and *tert*-butyl hydroperoxide (TBHP), the reaction between styrene and ethyl 2-pyridylacetate directly

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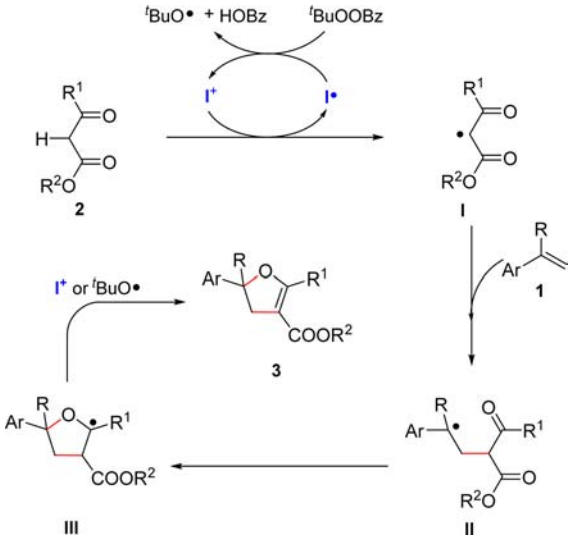
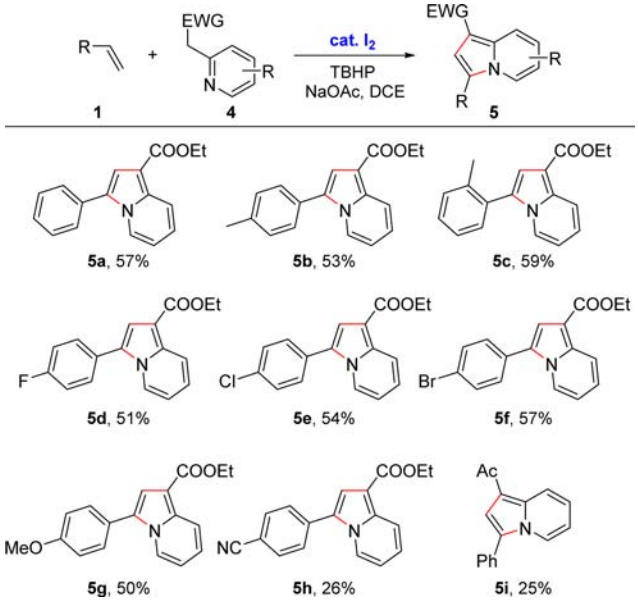
Scheme 3. Proposed Mechanism



furnished an indolizine ring formation product in a good selectivity (Scheme 4, **5a**). After obtaining the promising result,

Scheme 4. Substrate Scope of the I_2-Catalyzed Oxidative Cross-Coupling/Annulation of 2-Pyridinyl-β-esters with Alkenes[a]



[a]Reaction conditions: **1** (1.50 mmol), **4** (0.50 mmol), TBHP (1.50 mmol, 70% in aqueous solution), I_2 (0.10 mmol), NaOAc (0.50 mmol) in DCE (4.0 mL), 80 °C for 20 h.

we also turned to explore the substrate scope of this transformation. The *para*- and *meta*-methylstyrenes showed a reactivity similar to that of simple styrene under the standard condition (Scheme 4, **5b** and **5c**). It is worth noting that halide substituents such as F, Cl, and Br were well-tolerated and were crucial for further functionalization (Scheme 4, **5d**−**5f**). Electron-rich *p*-methoxystyrene was also tried, and a slightly decreased yield was obtained (Scheme 4, **5g**). Moreover, electron-deficient 4-vinylbenzonitrile afforded the desired product but with a lower yield (Scheme 4, **5h**). Compared with ethyl 2-pyridylacetate, 1-phenyl-2-propanone showed a decreased reactivity in this reaction system (Scheme 4, **5i**). Though the reaction efficiency is moderate in this transformation, our study on discovering the unique reactivity of iodine in achieving the oxidative coupling/annulation with alkenes is of great significance. Obviously, the reaction mechanism with 2-pyridinyl-β-esters would be similar to that of β-keto esters. Compared to the reaction with β-keto esters, the direct formation of indolizine indicated a facile oxidative dehydrogenation process after cyclization.[12]

In summary, we have developed an iodine-catalyzed oxidative coupling/annulation reaction for the construction of hydrofurans and indolizines in one step. A catalytic amount of molecular iodine in combination with peroxides was proven to be an effective alternative reaction system for excess transition metal oxidants in these transformations. The reaction was likely to go through a radical addition/cyclization mechanism. Various alkenes were able to couple with β-keto esters or 2-pyridinyl-β-esters through this reaction strategy. Synthetically, this iodine catalytic system could be scaled up to 20 mmol with good efficiency. Detailed mechanistic investigations and employing iodine catalysis in more oxidative annulation reactions are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details and spectral data for all compounds are provided. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00912.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aiwenlei@whu.edu.cn.

Author Contributions

§S.T. and K.L. contributed equally.

Notes

The authors declare no competing financial interest.

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