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I_2-Promoted Selective Oxidative Cross-Coupling/Annulation of 2-Naphthols with Methyl Ketones: A Strategy To Build Naphtho[2,1-*b*]furan-1(2*H*)-ones with a Quaternary Center

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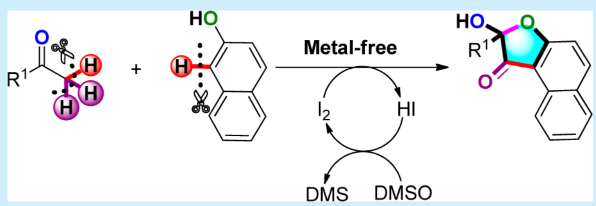
Supporting Information

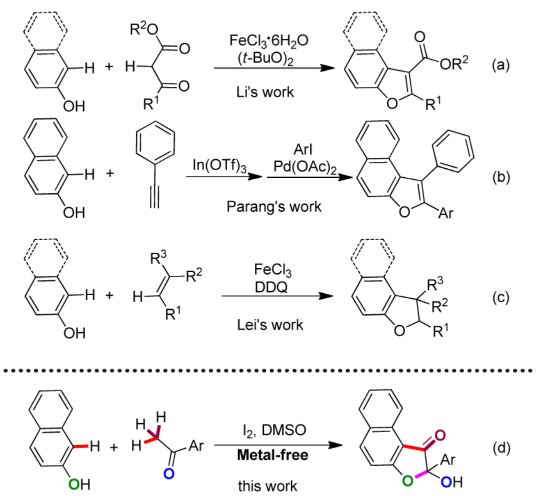
ABSTRACT: A highly efficient and selective molecular iodine-promoted oxidative cross-coupling/annulation between 2-naphthols and methyl ketones has been realized. The reaction successfully constructed a new quaternary carbon center within 3(2*H*)-furanones. Our synthetic strategy provided an in situ iodination-based oxidative coupling pathway. Based on the experimental results, a self-sequenced iodination/Kornblum oxidation/Friedel–Crafts/oxidation/cyclization mechanism was proposed.



The formation of a C–C bond is a key transformation in organic synthesis and has received widespread interest.[1] The study of novel methods for the construction of a C–C bond through direct C–H bond functionalization has thus attracted considerable attention in recent years, where significant progress has been achieved.[2] The oxidative cross-coupling approach, in which two C–H bonds are directly applied as nucleophiles,[3] has been recognized as one of the most efficient, atom-economical, and environmentally friendly strategies for the formation of a C–C bond.[4] Over the past few years, several types of C–H reagents have been applied in coupling reactions, such as *ortho*-directed Ar–H, terminal alkynes, alkenes, and specifically C_{sp3}–H.[5] However, further discoveries of different R–H as nucleophiles remains highly significant for organic molecule synthesis.

Phenols and naphthols are readily available and widely used chemical feedstock. Although oxidative phenol coupling has received considerable attention since the 1920s, the use of simple phenols in oxidative cross-couplings often yields homocoupling byproducts, higher molecular weight polymers, or C–O-connected phenol portions in addition to the desired product.[6] However, some pioneering examples of oxidative cross-coupling reactions between phenol and other nucleophiles have been reported. Importantly, a tandem oxidative coupling and annulation reaction of phenols and *β*-keto esters via a combination of $FeCl_3 \cdot 6H_2O$ and (*t*-BuO)$_2$ was successfully realized by Li and co-workers[7a] (Scheme 1a). Recently, Parang et al.[7b] described a sequential hydroarylation of naphthols and alkynes in the presence of In(OTf)$_3$, which was followed by Pd(OAc)$_2$-catalyzed one-pot Heck-oxyarylation of generated 1-substituted *α*-hydroxy (Scheme 1b). Most recently, the Lei group[7c] disclosed a highly selective oxidative coupling/cyclization reaction of phenols and olefins with catalytic amounts of $FeCl_3$ and DDQ as the oxidant (Scheme 1c). Despite these recent advances, the selective

Scheme 1. Oxidative Cross-Coupling Reactions between Phenol and Nucleophiles



oxidative cross-coupling with phenols as nucleophiles is still a fascinating topic. In this work, the first known example of a metal-free selective oxidative cross-coupling of 2-naphthols and methyl ketones is reported (Scheme 1d).

Notably, the development of transition-metal-free cross-coupling reactions is a highly topical and significant research area in chemical synthesis.[8] As an alternative strategy, it may address some of the aforementioned challenges. The key challenge here lies in the determination of how to activate C–H without the assistance of a transition metal. Radical activation could be an option. Recent developments with radical oxidative

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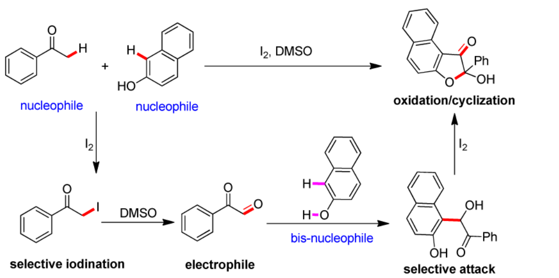
coupling processes in studies of C−C bond formation have been highly impressive and have provided some interesting alternatives to well-established methods for C−C formation.[9] On the other hand, only recently have researchers become interested in molecular iodine as catalysts in oxidative coupling reactions, and it turned out to be efficient mediators. The most important direct C−H bond activation step is thought to occur through the formation of a new carbon−iodine bond, which is known as the in situ iodination-based oxidative coupling pathway.[10] It is envisioned that if the selective iodination of C_{sp3}−H bond of acetophenone is feasible by molecular iodine, in situ oxidation of carbon−iodine bond could generate an electrophilic α-ketoaldehyde intermediate primed for selective attack by the C−H of 2-naphthols. Following oxidation, cyclization would furnish naphtho[2,1-*b*]furan-1(2*H*)-one with a quaternary carbon center as desired (Scheme 2). On

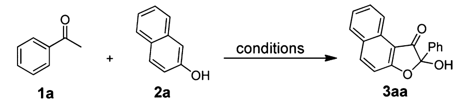
Scheme 2. Design Strategy: A Highly Selective I_2-Promoted Oxidative Coupling of 2-Naphthols with Methyl Ketones



the basis of this design, a highly efficient and selective molecular iodine-promoted oxidative coupling of 2-naphthols with methyl ketones is described here. This strategy provided a powerful and general route to the synthesis of 3(2*H*)-furanones, a privileged structure and prevalent motif in natural products and biologically active molecules.[11] It is worth mentioning that several synthetic methodologies of 3(2*H*)-furanones have already been established, including metal-mediated cyclization of alkynyl substrates, transformation from furans, cyclization of dienes or alkynes, and cycloisomerization of allenes.[12]

To test the above hypothesis, the present study was initiated with acetophenone (**1a**) and 2-naphthol (**2a**) as model substrates under various conditions. To our delight, the reaction occurred with 1.0 equiv of I_2 in DMSO at 100 °C for 48 h to afford the oxidative cross-coupling product **3aa** in 70% yield (Table 1, entry 1). The structure was unambiguously confirmed by X-ray crystallography analysis. When the dosage of I_2 was increased to 1.6, the yield greatly increased to 81% (Table 1, entry 3). However, further increases in the amount of I_2 did not lead to significant differences in the yield. The reaction was unable to occur in the absence of I_2 (Table 1, entry 5), indicating that molecular iodine was essential for the reaction to proceed. Friedel−Crafts alkylation is often performed in the presence of Brønsted or Lewis acid; the coupling reaction in this work thus used a variety of Brønsted and Lewis acid catalysts. Unfortunately, they were found unable to effectively promote the reaction (Table 1, entries 6−11). It was thus essential to establish a suitable base for the cyclization step. A variety of bases were examined and shown to yield poor results (Table 1, entries 12−17), which suggested that additional base could not enhance the catalytic efficiency of I_2. A range of different temperatures were subsequently scanned to improve the yield (Table 1, entries 18−22), where 100 °C

Table 1. Optimization of the Reaction Conditions[a]



entry	I_2 (equiv)	acid	base	temp (°C)	yield[b] (%)
1	1.0			100	70
2	1.2			100	75
3	**1.6**			**100**	**81**
4	2.0			100	79
5				100	0
6	1.6	CF_3SO_3H		100	78
7	1.6	PTSA		100	40
8	1.6	HOAc		100	42
9	1.6	$AlCl_3$		100	47
10	1.6	$ZnCl_2$		100	45
11	1.6	$FeCl_3$		100	76
12	1.6		Cs_2CO_3	100	21
13	1.6		K_2CO_3	100	16
14	1.6		KOH	100	18
15	1.6		pyridine	100	20
16	1.6		DBU	100	22
17	1.6		Et_3N	100	27
18	1.6			60	18
19	1.6			80	46
20	1.6			90	65
21	1.6			110	78
22	1.6			130	64
23[c]	1.6			100	60
24[d]	1.6			100	75

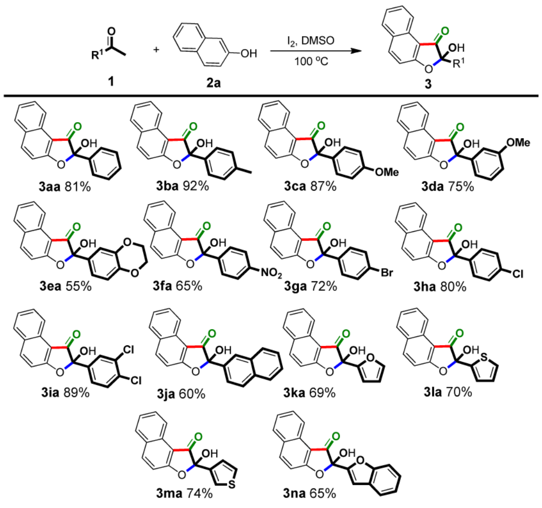
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), acid or base (1.0 mmol), solvent (4 mL). [b]Isolated yields. [c]**2a** (1.0 mmol). [d]**2a** (1.5 mmol).

was determined optimal for the cascade reaction. Finally, the addition of excess **2a** (2.0 equiv) was shown to provide the best outcome in **3aa**.

With the optimized conditions in hand, the generality and scope of the molecular iodine-promoted direct synthesis of 3(2*H*)-furanones was next explored. To our delight, the reaction demonstrated wide scope for the structure of aromatic ketones (Scheme 3). Aryl methyl ketones bearing electron-neutral (4-H, 4-Me), electron-rich (4-OMe, 3-OMe, 3,4-OCH_2CH_2O), and electron-deficient (4-NO_2) substituents were successfully converted directly into the corresponding products in moderate to excellent yields (55−92%; **3aa**−**fa**). The electronic and steric nature of aromatic ketones was shown to have little influence on the reaction efficiency. Much to our satisfaction, the conditions were found to be mild enough to be compatible with halogenated (4-Br, 4-Cl, 3,4-Cl_2) substrates (72−89%; **3ga**−**ia**), which provided the possibility for further functionalization. 2-Naphthyl methyl ketone subsequently provided the expected products **3ja** in 60% yield. However, heteroaryl ketones, including furanyl, thienyl, and benzofuryl, did not affect the overall efficiency, and the desired products were furnished in moderate to good yields (65−74%; **3ka**−**na**).

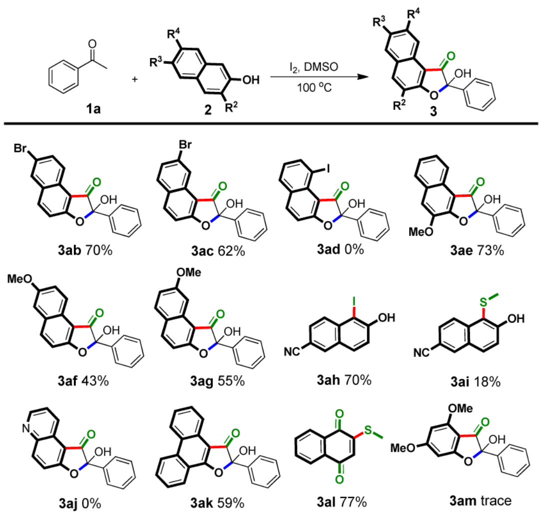
The scope of this reaction was subsequently extended to different substituted naphthol and phenol derivatives (Scheme 4). To our delight, the different bromo substituents at the C6 and C7 positions of 2-naphthol were well tolerated in the reaction, leading to bromo-substituted complex heterocyclic products (55, 92%; **3ab**, **3ac**; respectively). To our disappoint-

Scheme 3. Scope of Methyl Ketones[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (2.0 mmol), and I_2 (1.6 mmol) in DMSO (4 mL) at 100 °C. [b]Isolated yield.

Scheme 4. Scope of Naphthol and Phenol[a]

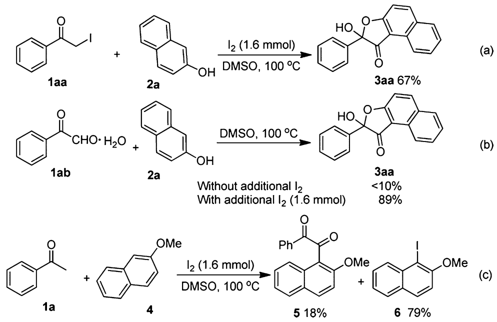


[a]Isolated yield.

ment, 8-iodonaphthalen-2-ol was unable to react with acetophenone **1a** to afford the desired products **3ad**. Moreover, *β*-naphthols with electron-donating groups were found to be effectual under the present reaction conditions, affording the corresponding products **3ae–ng** in 43–73% yields. Meanwhile, the electron-withdrawing moieties (6-CN) prevented the reaction from proceeding due to decreased electron density in the naphthyl ring, which produced the two products **3ah** and **3ai**. The electronic nature of the substrates was shown to strongly influence oxidative cross-coupling. Fortunately, it was found that phenanthren-9-ol could be applied to the transformation to generate **3ak** in 59% yield. On the other hand, 1-naphthol was found to be unstable under the reaction conditions, with 2-methylthionaphthoquinone **3al** isolated in 77% yield. Finally, a less activated phenol ring, such as 3,5-dimethoxylphenol, did not allow the reaction to occur and left only traces of the expected product **3am** in the crude mixture.

With the scope of the method established, the reaction mechanism was subsequently considered. When *α*-iodo acetophenone (**1aa**) and phenylglyoxal (**1ab**) were subjected to the standard reaction conditions, **3aa** was obtained in 67% and 89% yields, respectively (Scheme 5a, 5b). These results

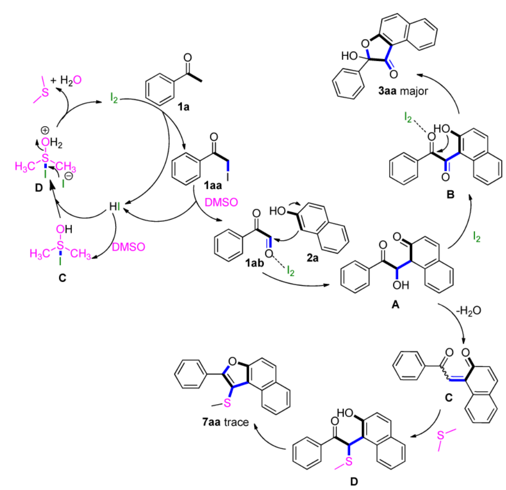
Scheme 5. Control Experiments



clearly confirmed phenacyl iodine **1aa** and phenylglyoxal **1ab** were the key intermediates in this transformation. However, **3aa** was not observed when **1ac** was tested in the absence of I_2 (Scheme 5b). This suggested that iodine played an important role in the Friedel–Crafts/annulation process. To our surprise, replacing *β*-naphthol with 2-methoxynaphthalene provided the expected product **5** in a low yield under the standard conditions, which was most likely due to the strong steric hindrance of methoxyl (Scheme 5c). The reaction mechanism was deemed consistent with the design strategy.

Based on previous reports[13] and the above results, a possible mechanism was proposed using acetophenone (**1a**) and 2-naphthol (**2a**) as an example (Scheme 6). The initial

Scheme 6. Possible Mechanism



elimination of HI from **1a** by molecular iodine generated *α*-iodo ketone in situ, which converted into phenylglyoxal and released HI after a subsequent Kornblum oxidation. The aldehyde group of **1ab** was then activated by excess or regenerated Lewis acid I_2. Next, **2a** could attack the activated aldehyde group of phenylglyoxal to produce the intermediate **A**, followed by further rapid oxidation by I_2 to afford **B**.[14] As a result, intermediate **B** underwent an intramolecular cyclization via an oxygen atom attacking to the *β*-carbonyl group and furnished the desired product **3aa** in the presence of iodine. Although the reoxidation of HI should be feasible,[15] this reaction was performed with stoichiometric amounts of iodine.

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In addition, 1-(methylthio)-2-phenyl-5,5a-dihydronaphtho[2,1-*b*]furan **7aa** was detected in this reaction system as it underwent a dehydration process to generate the intermediate *o*-QM **C**.[16]

In summary, a highly efficient and selective I_2-promoted oxidative cross-coupling/annulation has been developed with the direct use of 2-naphthols and methyl ketones as nucleophiles for the construction of naphtho[2,1-*b*]furan-1(2*H*)-one with a quaternary carbon center. Initial studies of the mechanism suggest that this reaction could have occurred through a self-sequenced iodination/Kornblum oxidation/Friedel−Crafts/oxidation/cyclization cascade reaction. Moreover, this tandem catalysis proved easy to operate and could sequentially promote three mechanistically distinct reactions in a single reactor with the use of molecular iodine. Further explorations of I_2-promoted oxidative coupling are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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