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Iodine-Promoted Oxidative Cross-Coupling of Unprotected Anilines with Methyl Ketones: A Site-Selective Direct C−H Bond Functionalization to C4-Dicarbonylation of Anilines

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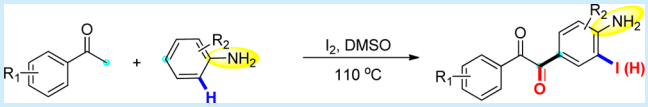
Supporting Information

ABSTRACT: An unprecedented direct dual C−H bond functionalization of unprotected anilines and methyl ketones has been demonstrated. It is the first example of iodine-promoted highly chemo- and site-selective oxidative C−H/C−H cross-coupling of anilines and methyl ketones to furnish the C4-dicarbonylation of anilines in moderate to good yields. Moreover, coproduct HI acted as a catalyst in the reaction. The salient feature of this approach is unprecedented C−H functionalization rather than N−H functionalization of unprotected anilines.



Amino-containing compounds are ubiquitous among biologically active molecules, natural products, and material sciences and can act as a potentially valuable synthetic intermediates in organic synthesis.[1] The development of green, atom-economic, and sustainable methods to build amino-containing compounds has always been a fascinating topic.[2] Direct oxidative coupling can avoid prefunctionalization of substrates and represents ideal chemical synthesis.[3,4] Anilines possessing an electron-rich aromatic ring can be used in oxidative couplings with C−H to build C−C and C−N bonds.[5] Recent advances have focused on the oxidative coupling of C−H with N−H in anilines to allow N-dicarbonylation of anilines to prepare α-ketoamides. Notably, Jiao and co-workers previously demonstrated an oxidative amidation−diketonization reaction of terminal alkynes with anilines (Scheme 1a).[6] They subsequently proposed a novel Cu-catalyzed C−H bond oxidative amidation to achieve diketonization of anilines via oxidative coupling of aryl acetaldehydes or α-carbonyl aldehydes with anilines (Scheme 1b).[7] Moreover, Wang et al.[8] developed an electrochemical oxidation of acetophenones with anilines to allow diketonization for construction of α-ketoamide compounds. This process proceeded via an anodic oxidation initiated by an iodine radical (Scheme 1c). These limited important examples, such as direct oxidative C_{sp^3}−H/C_{sp^2}−H of unprotected anilines and cross-coupling to C4-dicarbonylation of anilines, have not yet been reported. This is likely because carbon is a weaker nucleophile than nitrogen, especially the free N−H of anilines. Therefore, direct oxidative C_{sp^3}−H/C_{sp^2}−H cross-coupling of unprotected anilines to construct C−C rather than C−N bonds will be a greater challenge. In the present work, we present a highly chemo- and site-selective oxidative coupling of C_{sp^3}−H of methyl ketones and C_{sp^2}−H of anilines with free N−H to build *p*-aminophenyl diketones (Scheme 1d).

Based on our previous work on oxidative C_{sp^3}−H/N−H cross-coupling to build a C−N bond,[9] we accidentally found the formation of a new C−C bond via oxidative cross-coupling with acetophenone (**1a**) and aniline (**2a**) in the presence of 10 mol % of CuI and molecular iodine at 100 °C in DMSO (Table 1, entry 1). Moreover, the C−H bond at the *ortho*-position of aniline was serendipitously iodinated to give product 4-amino-3-iodophenyl diketone in 42% yield (Table 1, entry 1). This is a potentially useful compound because aryl iodides are broadly utilized to construct complex structures in organic syntheses via transition-metal-catalyzed coupling reactions (such as Suzuki coupling, Negishi coupling, and Buchwald/Hartwig amination/amidation).[10,11] Catalytic CuI was found to be unnecessary in subsequent reactions (Table 1, entry 2). Having obtained an initial and promising result, we next focused on optimization of the reaction conditions. We first examined the effect of different equivalents of **2a** and found that lowering the amount of **2a** resulted in improved yields (Table 1, entries 3 and 4), with the best result obtained with 0.8 equiv of **2a** (Table 1, entry 4).

Scheme 1. Dicarbonylation of Anilines

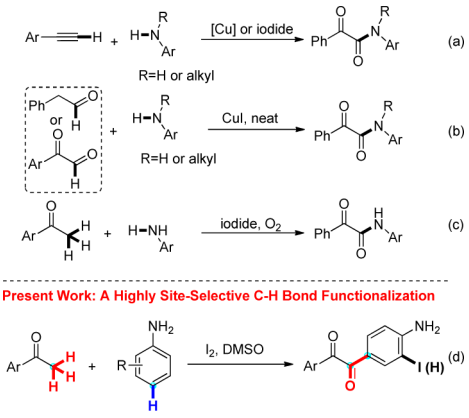


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Table 1. Optimization of the Reaction Conditions[a]

1a 2a 3aa

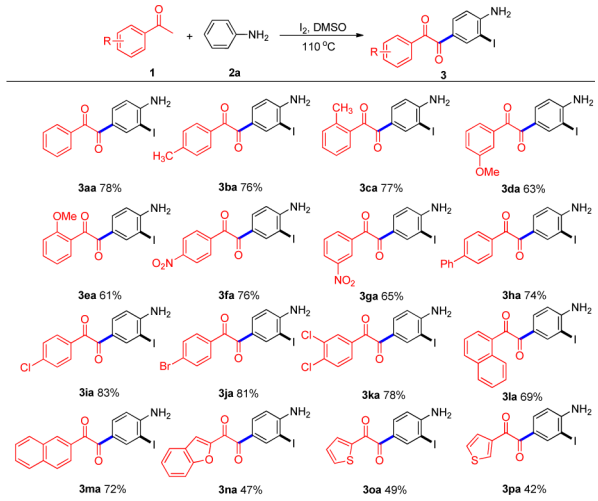
entry	2a (equiv)	iodine (equiv)	temp (°C)	acid	yield (%)[b]
1[c]	1.0	1.6	100		42
2	1.0	1.6	100		42
3	0.5	1.6	100		50
4	0.8	1.6	100		74
5	1.2	1.6	100		35
6	1.5	1.6	100		29
7	2.0	1.6	100		trace
8	0.8	1.6	60		trace
9	0.8	1.6	80		42
10	0.8	1.6	90		53
11	**0.8**	**1.6**	**110**		**78**
12	0.8	1.6	130		62
13	0.8	0	110		0
14	0.8	0.8	110		7
15	0.8	1.2	110		40
16	0.8	2.0	110		77
17	0.8	2.5	110		75
18	0.8	1.6	110	$TsOH·H_2O$	73
19	0.8	1.6	110	CF_3SO_3H	78
20	0.8	1.6	110	HCl	72
21	0.8	1.6	110	$FeCl_3$	70
22	0.8	1.6	110	$AlCl_3$	60
23	0.8	1.6	110	$Zn(OTf)_2$	57

[a]Reaction conditions: **1a** (1.0 mmol), **2a**, I_2, heated in 3 mL of DMSO within 12 h. [b]Products were obtained in isolated yields based on aniline. [c]10 mol % of CuI was used.

Increasing the equivalents of **2a** was detrimental to the yield (Table 1, entries 5−7). Temperature was tested between 60 and 130 °C and found to have an important influence on the reaction yield (Table 1, entries 8−12). Decreasing the I_2 dosage greatly decreased the yield (Table 1, entries 13−15). However, increasing the equivalents of I_2 did not lead to substantial differences in the yield (Table 1, entries 16 and 17). The reaction did not occur in the absence of I_2 or with other iodine sources (see Supporting Information), indicating that molecular iodine was essential for the reaction (Table 1, entry 13). A series of Brønsted and Lewis acids ($TsOH·H_2O$, CF_3SO_3H, HCl, $FeCl_3$, $AlCl_3$, and $Zn(OTf)_2$) were screened as additives for the reaction, and no benefit was found in promoting the reaction (Table 1, entries 18−23). The optimal conditions determined were **1a** (1.0 mmol) with **2a** (0.8 mmol) in the presence of I_2 (1.6 mmol) in DMSO at 110 °C to afford the desired product in 78% yield (Table 1, entry 11).

With optimized reaction conditions in hand, we investigated the substrate generality of this I_2-promoted oxidative coupling reaction with methyl ketone substrates. A series of substituted aryl methyl ketones were found to undergo the desired transformation to give the corresponding products in moderate to good yields (42−83%, Scheme 2). The electronic and steric nature of the aromatic ketones was shown to have little influence on the reaction efficiency. The presence of electron-neutral (4-H, 2-Me, 4-Me), electron-donating (2-OMe, 3-OMe), and electron-deficient (3-NO_2, 4-NO_2, 4-Ph) groups attached to the phenyl ring of the aryl methyl ketones had little effect on reactivity, and the corresponding *p*-aminophenyl diketones were afforded in

Scheme 2. Scope of Aryl Methyl Ketones and Aniline[a]

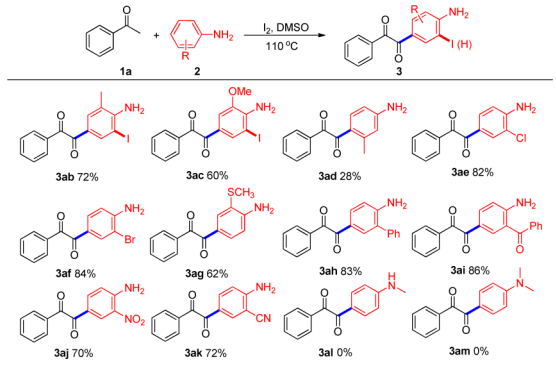


[a]Reaction conditions: **1** (1.0 mmol), **2a** (0.8 mmol), I_2 (1.6 mmol) in DMSO (3 mL) at 110 °C within 12 h. Isolated yield based on aniline.

good yields (61−78%, **3aa**−**ha**). The optimized conditions were also compatible with aromatic ketones bearing halogen substituents (4-Cl, 4-Br, 3,4-Cl_2), with the corresponding products **3ia**−**ka** obtained in 78−83% yields. The structure of compound **3ja** was determined by X-ray crystallographic analysis (see Supporting Information). Sterically hindered 1-acetylnaphthalene (**1l**) and 2-acetylnaphthalene (**1m**) also furnished the desired products **3la** and **3ma** in 69 and 72% yields, respectively. Heteroaryl methyl ketones, benzofuryl (**1n**), and two thiophenyl compounds (**1o**, **1p**), were investigated under the optimized conditions and resulted in the corresponding products **3na**−**3pa**, albeit in moderate yields (42−49%).

We next investigated using substituted anilines as substrates to further expand the scope of our coupling. The results are displayed in Scheme 3. *o*-Toluidine and 2-methoxyaniline

Scheme 3. Scope of Acetophenone and Anilines[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (0.8 mmol), I_2 (1.6 mmol) in DMSO (3 mL) at 110 °C within 12 h. Isolated yield based on anilines.

performed well, giving the desired products **3ab**−**ac** in 60−72% yield. Notably, *meta*-substituted aniline **2d** yielded product **3ad** in 28% isolated yield under the standard conditions. This result indicates that the steric nature of the aniline has a major influence on the reaction efficiency. The position of substituents on the aniline also had a significant influence on the C−H bond iodination. The formation of non-iodinated product **3ad** also implies that the selective C−H iodination occurs before the

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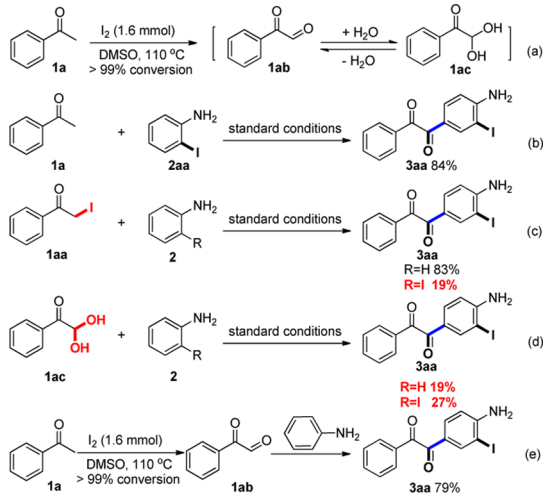
oxidative C_{sp^3}–H/C_{sp^2}–H cross-coupling of aniline. Halogen-substituted anilines (2-Cl, 2-Br) afforded the oxidative coupling products in moderate to good yields (82–84%, **3ae–af**). A diverse range of groups (2-SCH_3, 2-Ph, 2-PhCO, 2-NO_2, 2-CN), including an electron-withdrawing group attached to the phenyl rings, exhibited excellent reactivity (62–86%) to give non-iodinated products **3ag–ak**. These results indicate that the electron density of the phenyl ring of anilines has an important effect on the iodinated reaction. Unfortunately, the reaction of N-substituted arylamines with acetophenone failed to give the desired products under the standard conditions (**3al–am**), indicating that unprotected anilines are required for this transformation.

With the scope of the method established, the reaction mechanism was investigated. Aryl methyl ketone **1a** (1.0 mmol) was heated with I_2 (1.6 mmol) in DMSO at 110 °C to give phenylglyoxal **1ab** and the corresponding hydrated species **1ac** in quantitative yield (Scheme 4a). Reaction of acetophenone **1a**

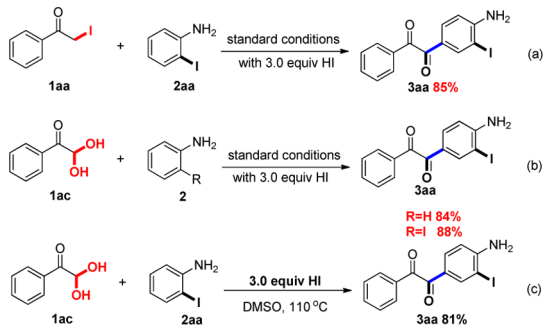
Scheme 4. Control Experiments



with 2-iodoaniline **2aa** was successful, and product **3aa** was obtained in good yields (Scheme 4b). Substrates **1aa** (1.0 mmol) and **2a** (0.8 mmol) were treated with I_2 (1.6 mmol) at 110 °C in DMSO, and the desired product **3aa** was obtained in 83% yield (Scheme 4c). These results clearly confirmed the intermediacy of 2-iodoaniline **2aa** and phenacyl iodine **1aa** in the transformation. However, reacting α-iodoacetophenone **1aa** with 2-iodoaniline **2aa** in DMSO at 110 °C gave **3aa** in only 19% yield (Scheme 4c). Moreover, when the reaction of phenylglyoxal **1ac** with aniline **2a** or 2-iodoaniline **2aa** was performed under the standard conditions, product **3aa** was obtained in a lower yield (Scheme 4d). To our surprise, converting **1a** (1.0 mmol) to **1ab** by treatment with I_2 (1.6 mmol) in DMSO (3 mL) at 110 °C for 1 h, with subsequent addition of **2a** (0.8 mmol) with 7 h heating, gave the desired product **3aa** in 79% yield (Scheme 4e).

We further experimented to develop a better understanding of the reaction mechanism and explain the above experimental results. We postulated that coproduct HI may act as an important promoter in the reaction. The successful reaction of α-iodoacetophenone **1aa** with 2-iodoaniline **2aa** with additional HI supports this hypothesis (Scheme 5a). Furthermore, in the presence of iodine and additional HI, hydrated hemiacetal **1ac** reacted with aniline **2a** or 2-iodoaniline **2aa** to afford the oxidative coupling product **3aa** in 84 and 88% yield, respectively

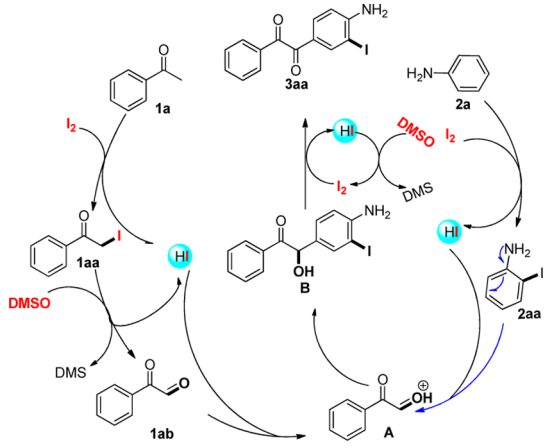
Scheme 5. Control Experiments



(Scheme 5b).[12] Hydrated hemiacetal **1ac** could react with aniline **2aa** smoothly using 3.0 equiv of HI (Scheme 5c). These results further confirmed the intermediates phenacyl iodine **1aa**, 2-iodoaniline **2aa**, and phenylglyoxal **1ac** in the transformation. In addition, these results emphasized the crucial role of coproduct HI in the subsequent domino process.

On the basis of our results and previous reports,[9,13] we proposed a mechanism for this I_2-catalyzed highly chemo- and site-selective oxidative cross-coupling using acetophenone **1a** and aniline **2a** (Scheme 6). The initial reaction of aniline **2a** with

Scheme 6. Proposed Mechanism



I_2 can afford 2-iodoaniline **2aa**. Substrate **1a** with molecular iodine results in the formation of the α-iodoketone **1aa**, which is converted to phenylglyoxal **1ab** and releases HI by a subsequent Kornblum oxidation.[14] The aldehyde group of phenylglyoxal **1ab** is activated by coproduct HI to give positively charged **A**, which is trapped in situ by **2aa** via a Friedel–Crafts-type reaction to give intermediate **B**. Intermediate **B** is rapidly oxidized by I_2 to afford the desired product **3aa**.[13]

In summary, a highly chemo- and site-selective I_2-promoted oxidative cross-coupling for the dicarbonylation of anilines to prepare *p*-aminophenyl diketones under mild conditions has been established. This work provides the first approach for the construction of novel *p*-aminophenyl diketone skeletons by directly utilizing C_{sp^3}–H of methyl ketones and C_{sp^2}–H of anilines as nucleophiles to construct new C–C bonds. Further studies to elucidate a detailed mechanism and identify synthetic applications for this protocol are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01162.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data for **3ja** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) In the presence of additional HCl or HBr under standard conditions, hydrated hemiacetal **1ab** could react with 2-iodoaniline **2aa** and afford the oxidative coupling product **3aa** in 59 and 61% yield, respectively.

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