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Diamination/Oxidative Cross-Coupling/Bicyclization of Anilines and Methyl Ketones: Direct I_2-Promoted Synthesis of 1,2-Fused Oxindoles

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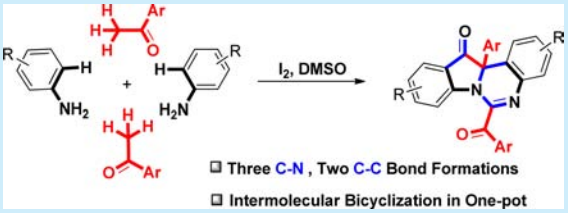
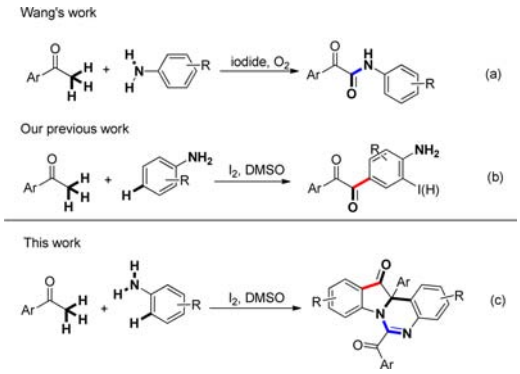
Supporting Information

ABSTRACT: An I_2-promoted domino bicyclization approach via multiple sequential C−H functionalization was serendipitously discovered for the synthesis of 1,2-fused oxindoles from methyl ketones and anilines. This approach was optimized, resulting in a concise and atom-economical approach for the one-pot construction of 1,2-fused oxindoles from methyl ketones and anilines rather than using preexisting indolin-3-ones or indoles. Mechanistic studies revealed that the key step involved an oxidative cross-coupling between in situ generated phenylglyoxal and α,α-diaminoketone.



Direct C−H bond functionalization represents an efficient, atom-economic, ideal chemical synthesis which avoids prefunctionalization of substrates.[1,2] Significant progress has been made during the past decade toward the development of C−H functionalization for the facile construction of C−C and C−N bonds.[2] Among them, the synthesis of N-aromatic compounds via the N−H/C−H functionalization of aromatic amines has been exploited extensively because of the ubiquitous nature of nitrogen-containing compounds in natural products, pharmaceuticals, and materials science.[3] Several elegant examples of the synthesis of N-bearing aromatic compounds have recently been reported involving the oxidative coupling of C−H with N−H or C−H in aromatic amines, as exemplified by the research groups of Jiao,[4] Antonchick,[5] and several others.[6] Notably, there has been considerable progress toward the development of metal-free processes for the oxidative coupling of methyl ketones with primary anilines. Wang et al. developed an oxidative N−H/C−H cross-coupling of anilines and acetophenones, resulting in the diketonization of the aniline via an anodic oxidation, which was initiated by an iodine radical (Scheme 1a).[7] This particular reaction therefore provided a new and efficient method for the coupling of acetophenones and amines to give a C−N bond. We previously reported the first example of the I_2-promoted oxidative C−H/C−H cross-coupling of anilines and methyl ketones to give 4-aminobenzils via the formation of a new C−C bond (Scheme 1b).[8] While both of these procedures represent important additions to the broad range of existing C−H functionalization methods, they are only capable of the formation of a single C−C or C−N bond. Furthermore, there have been no reports in the literature to date pertaining to the simultaneous formation of multiple C−C and C−N bonds from primary anilines and methyl ketones to allow for the one-pot construction of N-containing aromatic compounds. The development of a reaction of this type would therefore be highly desirable.

Scheme 1. Metal-Free Oxidative Coupling of Anilines with Methyl Ketones



As part of our ongoing interest in oxidative coupling as a general strategy for the construction of C−X (X = C,N) bonds and heterocycles,[8,9] we accidentally found the formation of 6-benzoyl-2,10-dimethyl-12a-phenylindolo[1,2-*c*]quinazolin-12-(12a*H*)-one when acetophenone (**1a**, 0.5 mmol) with I_2 (0.8 mmol) was mixed in DMSO (2 mL) at 100 °C for 50 min, followed the addition of *p*-toluidine (**2a**, 0.5 mmol) and further heating at 100 °C for 30 min (Table 1, entry 1). The structure of **3a** was unambiguously confirmed using X-ray crystallography (see Supporting Information, Figure S3). Herein, we present a new method for the I_2-promoted domino bicyclization via multiple sequential C−H functionalization reactions between the aniline and methyl ketone to 1,2-fused oxindoles (Scheme 1c). It is noteworthy that 1,2-fused oxindoles are widespread in natural alkaloids and biologically active molecules, highlighting the potential application of this new method.[10] In contrast to

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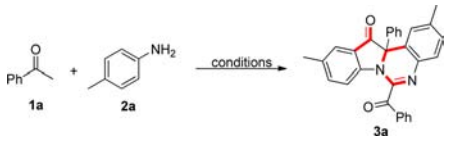
Table 1. Optimization of the Reaction Conditions[a]



entry	temp (°C)	I_2 (equiv)	acid (1.0 equiv)	yield (%)[b]
1	100	1.6		62
2	60	1.6		16
3	80	1.6		21
4	90	1.6		54
5	110	1.6		68
6	120	1.6		66
7	130	1.6		35
8	110	0.5		13
9	110	0.8		34
10	110	1.0		56
11	**110**	**1.2**		**70**
12	110	2.0		65
13	110	1.2	CF_3SO_3H	43
14	110	1.2	$TsOH·H_2O$	68
15	110	1.2	HOAc	40
16	110	1.2	HCl	45
17	110	1.2	$AlCl_3$	28
18	110	1.2	$ZnCl_2$	61
19	110	1.2	$FeCl_3$	31
20	110	1.2	$Zn(CF_3SO_3)_2$	59

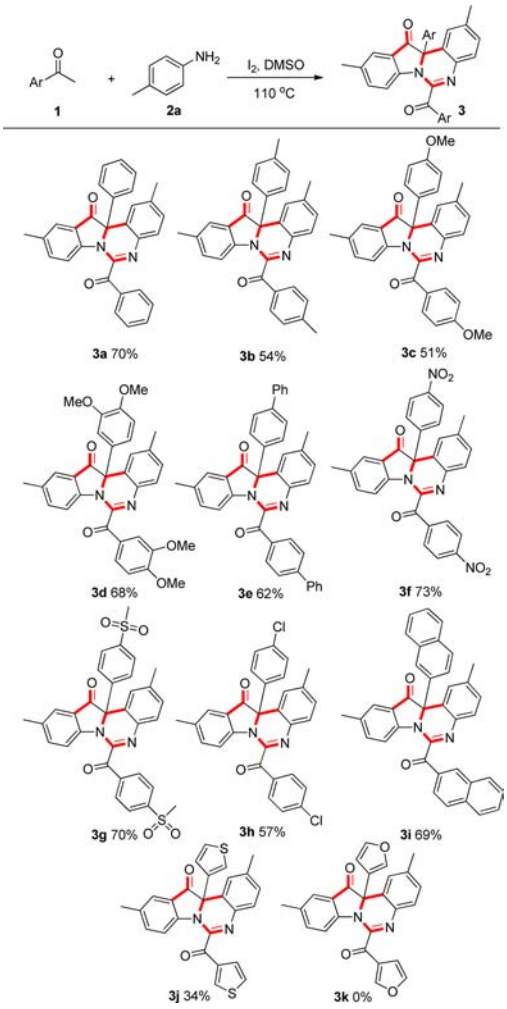
[a]Reaction conditions: **1a** (0.5 mmol), iodine were heated in DMSO (2 mL); after disappearance of the reactant **1a** (monitored by TLC), **2a** (0.5 mmol) was added. [b]Isolated yields.

previous reports pertaining to the synthesis of 1,2-fused oxindoles from preexisting indolin-3-ones or indoles,[11] this new method allows for the concise synthesis of 1,2-fused oxindoles from readily available methyl ketones and anilines in one pot.

Having obtained an unexpected and promising result, we proceeded to investigate the effects of different reaction parameters on the outcome of the reaction. We initially evaluated a range of different temperatures (Table 1, entries 2−7) and found that 110 °C was the optimum temperature for the domino annulation reaction. The reaction was further optimized by varying the number of equivalents of iodine (Table 1, entries 8−12). Iodine was found to play a critical role in the outcome of the reaction, as exemplified by the considerable decrease observed in the yield of the reaction as the amount of iodine was reduced from 1.0 to 0.5 equiv (Table 1, entries 8−10). Further experiments revealed that the optimum iodine charge was 1.2 equiv (Table 1, entry 11). Friedel−Crafts reactions are typically performed in the presence of a Brønsted or Lewis acid. In light of the similarities between these transformations, we conducted the current coupling reaction in the presence of a variety of different acids; however, none of them had a positive impact on the outcome of the reaction (Table 1, entries 13−20).

With the optimized conditions in hand, we proceeded to evaluate the scope and generality of this iodine-promoted domino annulation reaction via multiple direct C−H bond functionalization reactions. Pleasingly, the reaction demonstrated wide substrate scope in terms of the aromatic ketone unit (Scheme 2). Aryl methyl ketones bearing an electron-neutral (4-H), electron-donating (e.g., 4-Me, 4-OMe, 3,4-

Scheme 2. Scope of Methyl Ketones[a,b]



[a]Reaction conditions: **1** (1.0 mmol), iodine (1.2 mmol) were heated in DMSO (2 mL) for 50 min; **2a** (1.0 mmol) was added and heated for another 0.5 h. [b]Isolated yields.

$(OMe)_2$), or electron-withdrawing (e.g., 4-Ph, 4-NO_2, 4-SO_2CH_3) substituent on their phenyl ring were successfully converted to the corresponding products in moderate to good yields (51−73%; **3a−g**). Notably, the optimized conditions were compatible with a halogenated aryl methyl ketone (4-Cl) (57%; **3h**), which provided the possibility for further functionalization. Meanwhile, sterically hindered 2-naphthyl methyl ketone provided the expected product **3i** in 69% yield. The optimized conditions were also applied to thienyl methyl ketone, which gave the corresponding product **3j** in 34% yield. Unfortunately, however, the application of the standard conditions to furanyl methyl ketone failed to afford any of the desired product **3k**. The failure of this reaction could be attributed to the ring opening of furan under the acidic conditions.

The scope of this reaction was subsequently extended to a variety of substituted anilines, which gave the desired products in satisfactory yields (Scheme 3). Both electron-rich and electron-deficient anilines reacted smoothly to give the desired products in moderate to good yields (51−72%; **3l−o**). Anilines bearing electron-donating groups were found to be more reactive than those bearing electron-withdrawing substituents. Notably, an aniline substrate bearing a halogen substituent was

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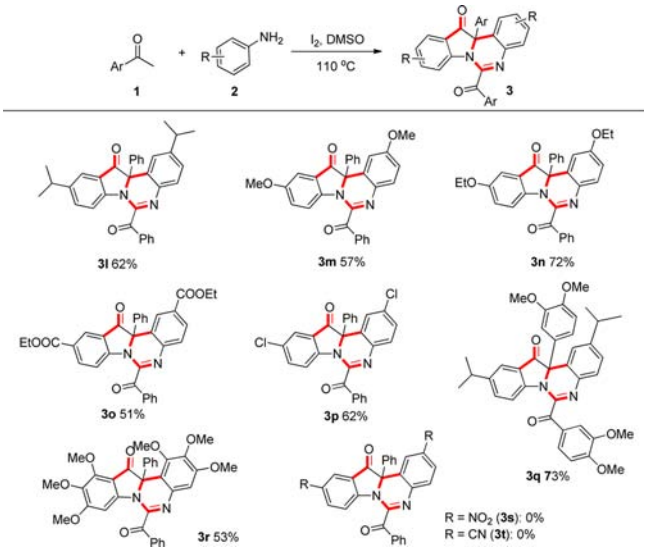
Scheme 3. Scope of Arylamine[a,b]

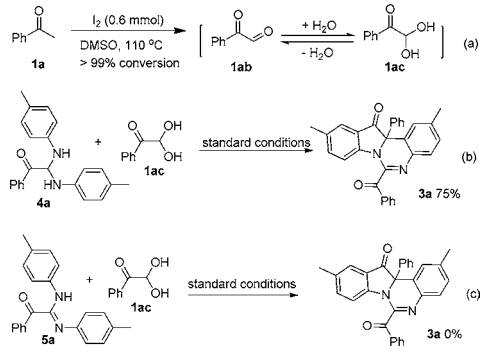


[a]Reaction conditions: **1** (1.0 mmol), iodine (1.2 mmol) were heated in DMSO (2 mL) for 50 min; **2** (1.0 mmol) was added and heated for another 0.5 h. [b]Isolated yields.

well tolerated, affording the expected halo-substituted product **3p** in 62% isolated yield, thereby provided an opportunity for further functionalization. 4-Isopropylaniline also reacted smoothly with an aryl methyl ketone bearing two electron-donating groups (3,4-$(OMe)_2$) to give the corresponding product **3q** in 73% yield. Aniline bearing three electron-donating groups at its 3-, 4-, and 5-positions gave the corresponding product **3r** in 53% yield. However, anilines bearing a strongly electron-withdrawing substituent at the 4-position of their phenyl ring (i.e., 4-NO_2 and 4-CN) failed to afford the corresponding products **3s** and **3t** under the standard conditions. This failure was attributed to the fact that Friedel–Crafts-type reactions generally require electron-donating substituents on the aromatic ring of the substrate.

Having established the scope of this new method, we proceeded to investigate the reaction mechanism by performing a series of control experiments. The reaction of acetophenone (**1a**) with I_2 in DMSO at 110 °C gave phenylglyoxal (**1ab**) and the corresponding hydrated species (**1ac**) in quantitative yield (Scheme 4a). The subsequent reaction of **4a**[12] (see Supporting Information) with **1ac** under the standard conditions gave the desired product **3a** in 75% yield (Scheme 4b). This result clearly confirmed that **4a** was the main intermediate in this

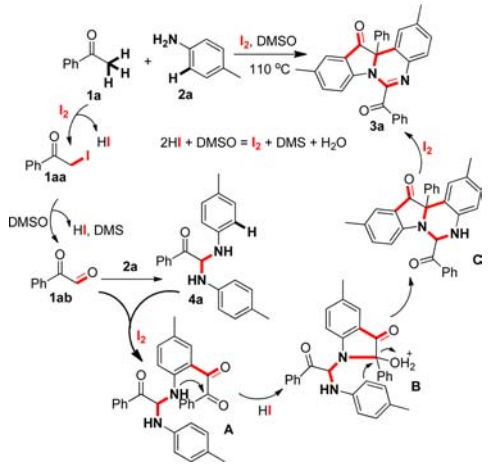
Scheme 4. Control Experiments



transformation. In contrast, the desired product **3a** was not detected when 2-oxo-acetamidine **5a**[13] was reacted with **1ac** under the same conditions (Scheme 4c), indicating that **5a** is not an important intermediate in this reaction.

Based on the results presented above, and the results of previous reports,[8,14] we proposed a plausible mechanism for this reaction using acetophenone (**1a**) and *p*-toluidine (**2a**) as representative examples (Scheme 5). The initial reaction of **1a**

Scheme 5. Possible Mechanism



with I_2 would result in the formation of α-iodoacetophenone (**1aa**), which would be subsequently converted to phenylglyoxal (**1ab**) with the concomitant release of HI in the presence of DMSO via a Kornblum oxidation reaction.[15] 1-Phenyl-2,2-bis(*p*-tolylamino)ethanone (**4a**) would then be formed by the reaction of 2 equiv of *p*-toluidine (**2a**) with 1 equiv of **1ab**. The aldehyde group of another equivalent of phenylglyoxal (**1ab**) would then be trapped in situ by **4a** via a Friedel–Crafts-type reaction to give intermediate **A**.[14] The subsequent intramolecular annulation of intermediate **A** would give intermediate **B**, which would also undergo an intramolecular Friedel–Crafts-type alkylation via the coordination of the coproduct HI, formal S_N1 reaction, to form intermediate **C**. This step first generates a carbenium ion through dehydration of **B** (see Supporting Information, Figure S2, involving the formation of an iminium ion intermediate from **A**). Finally, intermediate **C** would undergo an oxidation reaction to give the desired product **3a** in the presence of excess or regenerated iodine.[16]

In summary, we have developed a novel I_2-promoted domino bicyclization involving multiple sequential C–H functionalization reactions between anilines and methyl ketones, leading to the formation of three C–N bonds and two C–C bonds. This approach represents the first example of a tandem oxidative cross-coupling/annulation reaction sequence between anilines and methyl ketones for the direct synthesis of indolo[1,2-*c*]quinazolin-12(12a*H*)-one. Initial mechanistic studies suggested that this reaction most likely proceeds via an iodination/Kornblum oxidation/diamination/Friedel–Crafts/bicyclization cascade reaction. Further studies toward determining a detailed mechanism and further applications for this methodology are currently under way 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.6b03636.

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

X-ray crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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