ORGANIC LETTERS

2012
Vol. 14, No. 13
3392–3395

Metal-Free sp^3 C−H Bond Dual-(Het)arylation: I_2-Promoted Domino Process to Construct 2,2-Bisindolyl-1-arylethanones

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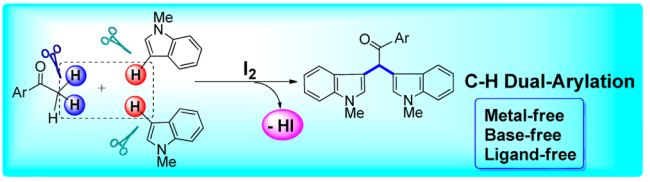
Received May 17, 2012

ABSTRACT



A molecular I_2-promoted sp^3 C−H bond dual-(het)arylation protocol was developed for the synthesis of 2,2-bisindolyl-1-arylethanones. Through a logical design, three mechanism-different reactions (iodination, Kornblum oxidation, and Friedel−Crafts reaction) were assembled in a single reactor. A variety of 2,2-bisindolyl-1-aryl ethanones were synthesized from simple and readily available aryl methyl ketones and indoles. In the reaction, metal, base, and ligand were all avoidable.

In recent years, direct arylation of the C−H bond has emerged as a hot theme in organic synthetic chemistry.[1] Many impressive results have been achieved for arylation of Csp−H and Csp^2−H bonds during the past several years.[2] However, reactions involving the Csp^3−H bond have suffered inherent problems due to inertia and weak coordination. Some efforts have been made to overcome the challenges (Scheme 1). The most widely used method is the coupling of Csp^3−H bonds with aryl halide or aryl metal. This method was demonstrated very well by Yu, Daugulis, Corey, Sames, Sanford, and Chen (Scheme 1, pathways A and B).[3] The intramolecular direct arylation was closely studied by Fagnou, Fujii and Ohno, and Chen (Scheme 1, pathway C).[4] The cross-dehydrogenative coupling (CDC) reaction is an excellent method for C−H arylation, which was efficiently launched by Li and others (Scheme 1, pathway D).[5] However, the scope of the substrates was limited since the sp^3 C−H bond must be

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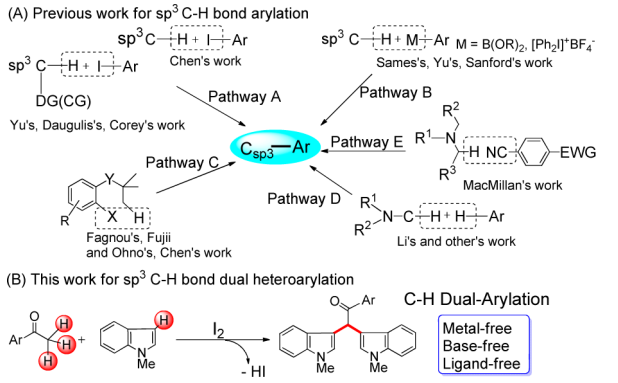
10.1021/ol301366p
Published on Web 06/26/2012

Scheme 1. Protocols for sp^3 C−H Bond Arylation



adjacent to a nitrogen or an oxygen atom. Recently, MacMillan proposed a graceful photoredox amine C−H arylation, which provides a new insight into C−H arylation (Scheme 1, pathway E).[6] The previous studies mainly focused on Pd-, Ru-, Cu-catalyzed arylation. Therefore, development of a metal-free C−H and C−H bond coupling protocol is still greatly desired for sp^3 C−H bond arylation.

Indoles are important molecules and exist widely in natural products and pharmaceuticals.[7] In addition, they have been known to be useful in agricultural chemistry and material science. Accordingly, synthesis and functionalization of indoles have attracted considerable attention over one and a half centuries.[8] Among them, bisindoles as molecular stars were pursued by many synthetic chemists and pharmacologists.[9] However, direct sp^3 C−H bond dual heteroarylation has not yet been proposed for the synthesis of bisindoles. As a part of our program aimed at constructing diverse heterocycles, we herein report a molecular I_2-promoted sp^3 C−H bond dual-(het)arylation protocol for accessing 2,2-bisindolyl-1-arylethanones from aryl methyl ketones and indoles.

Initially, the reaction conditions were optimized for dual heteroarylation of aryl methyl ketone (**1a**) with *N*-methylindole (**2a**). Various catalysts, additives, and temperatures were examined in DMSO, and all cases are shown in Table 1. To our delight, the reaction of **1a** with *N*-methylindole (**2a**) performed smoothly with 50% yield in the presence of I_2 (1.1 mmol) and CuO (1.1 mmol) at 80 °C in DMSO. Thus, we screened a series of Brønsted acids for this reaction, such as HOAc, $MeSO_3H$, CF_3SO_3H, TFA, PTSA (Table 1, entries 2−6), but the desired product **3aa** was obtained in a low yield. Alternatively, the diversity of Lewis acids were also investigated for the reaction. Gratifyingly, the reaction occurred in good yield by use of Ti(*i*-PrO)$_4$ and $ZnCl_2$ (Table 1, entries 7 and 9). However, other Lewis acids, such as $AlCl_3$, $FeCl_3$, $InCl_3$, and $Cu(OTf)_2$, only promoted this reaction in moderate yield. To our surprise, the reaction could perform in good yield in the absence of CuO and Lewis acid (Table 1, entry 13). However, the reaction could not perform at all without I_2 (Table 1, entry 14). After several experimental optimizations, we found that **1a** (1.0 mmol) could react with **2a** (2.0 mmol) in the presence of I_2 (1.0 mmol) in DMSO at 95 °C to afford the desired product in 76% yield (Table 1, entry 16).

Table 1. Optimization Studies for the Synthesis of 2,2-Bis(1-methyl-1*H*-indol-3-yl)-1-phenylethanone[a,b]

entry	I_2 (mmol)	CuO (mmol)	cat.	temp (°C)	time (h)	yield (%)
1	I_2 (1.0)	CuO (1.0)		80	10	50
2	I_2 (1.0)	CuO (1.0)	HOAc	80	12	<15
3	I_2 (1.0)	CuO (1.0)	$MeSO_3H$	80	12	<15
4	I_2 (1.0)	CuO (1.0)	CF_3SO_3H	80	12	<15
5	I_2 (1.0)	CuO (1.0)	PTSA	80	12	<15
6	I_2 (1.0)	CuO (1.0)	TFA	80	8	0
7	I_2 (1.0)	CuO (1.0)	Ti(*i*-PrO)$_4$	80	5	72
8	I_2 (1.0)	CuO (1.0)	$AlCl_3$	80	6	50
9	I_2 (1.0)	CuO (1.0)	$ZnCl_2$	80	4	74
10	I_2 (1.0)	CuO (1.0)	$InCl_3$	80	8	55
11	I_2 (1.0)	CuO (1.0)	$Cu(OTf)_2$	80	6	58
12	I_2 (1.0)	CuO (1.0)	$FeCl_3$	80	10	56
13	I_2 (1.0)			90	5	70
14				90	12	0
15	I_2 (1.0)			100	2	68
16	I_2 (1.0)			95	3	76
17	I_2 (1.5)			95	3	75

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), catalyst (0.03 mmol, 30 mol %), heated in 3 mL of DMSO. [b] Isolated yield.

Under the optimal conditions, a wide range of aryl methyl ketones was investigated. As shown in Scheme 2, the substituted aryl methyl ketones performed smoothly with *N*-methylindole **2a** to afford the desired products in moderate to good yields (58−85%). The electron-donating groups, such as 4-Me, 4-OMe, 2,4-(OMe)$_2$, and 3,4-OCH_2O, attached to phenyl rings of aryl methyl ketones exhibited good reactivity (Scheme 2, **3ba**−**ea**). The electron-withdrawing groups, such as Cl, Br, and NO_2, could

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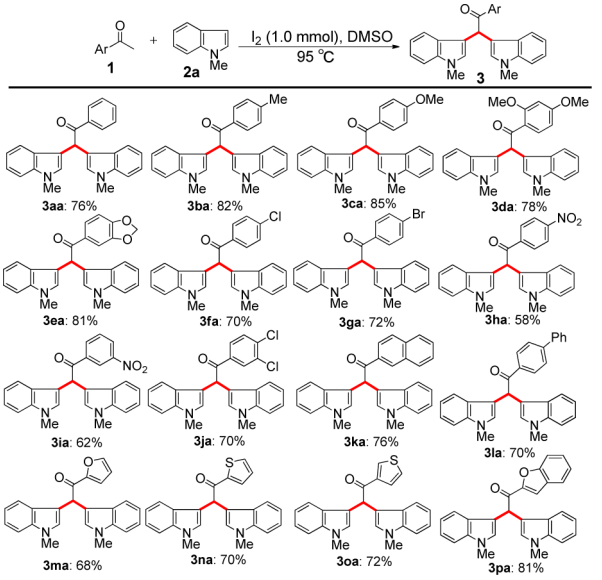
slightly decrease the reactivity (Scheme 2, **3fa**−**ja**). Furthermore, 2-naphthyl methyl ketone (**1k**) and biphenyl methyl ketone (**1l**) also reacted with *N*-methylindole **2a** to obtain satisfying results (76% and 70% yields). Encouraged by the results, the heteroaryl methyl ketones were investigated under the optimal conditions. To our delight, the substrates with heterocycle, such as furanyl (**1m**), thiophene-yl (**1n**, **1o**), and benzofuryl (**1p**), could obtain the corresponding products **3ma**−**pa** in moderate to good yields (68%-81%). As we know, compounds with multi-heterocyclic scaffolds are novel and important that would have enhanced biological activity or vagarious property. The bisindole molecules containing furan or thiophene or benzofuran were rarely reported in the literature.

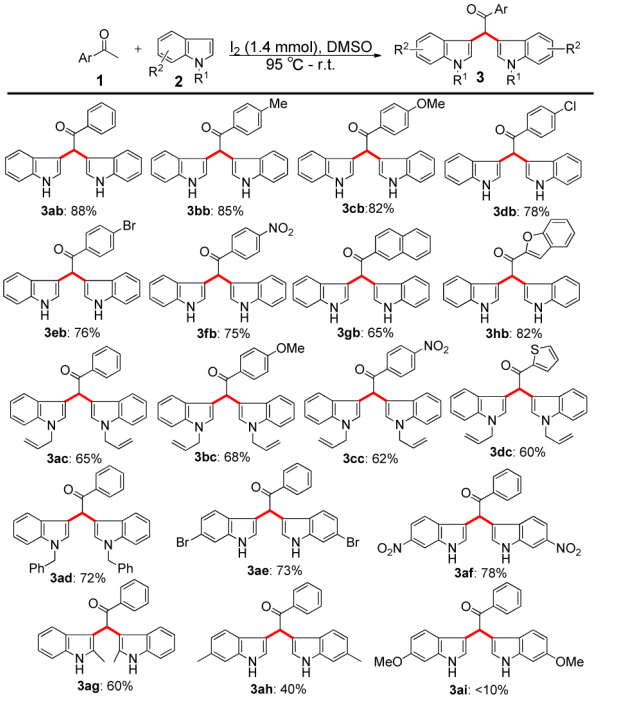
Scheme 2. Scope of Aryl Methyl Ketones and *N*-Methylindole



To further expand the scope of the substrates, diversity of indole derivatives were examined. To our disappointment, the reaction of acetophenone **1a** with indole **2b** provided a low yield. We observed that the desired products were obtained in moderate yield for the first 2 h, but some of the desired product decomposed over time. After several experimental iterations, we found that heating acetophenone **1a** in the presence of I_2 (1.4 mmol) at 95 °C for 2 h, then adding indole **2b** (2.0 mmol) and stirring at 25 °C for 2 h yielded the desired product in good yield (88%).

Under the optimal conditions, a series of indole derivatives was examined. Gratifyingly, indole **2b** could smoothly react with aryl methyl ketones to afford the corresponding products in good yields (Scheme 3, Entries **3ab**−**hb**). Both electron-donating and electron-withdrawing groups attached to the phenyl rings of **1a** could afford the corresponding products in moderate to good yields (65−88%). The *N*-allylindole **2c** and *N*-benzylindole **2d** could also perform smoothly to afford the corresponding products under these conditions (Scheme 3, entries **3ac**−**ad,** 60−72%). Encouraged by the above results, we turned our attention to the indole derivatives (**2e**−**i**), in which the substituted groups attached to the phenyl rings. Notably, the electronic properties of indole derivatives (**2e**−**i**) have strong influence on the yield. The electron-withdrawing groups attached to the phenyl rings of indole derivatives **2h**,**i** could give good yields (Scheme 3, **3ae** and **3af**). However, the electron-donating groups, such as 6-Me and 6-OMe, could largely decrease the reactivity to afford the desired products in very low yields (**3ah** and **3ai**). Furthermore, the target compounds **3ca** and **3db** were further determined by X-ray crystallographic analysis (Figures S1 and S2, Supporting Information).

Scheme 3. Scope of Aryl Methyl Ketones and Indoles



To gain some insights into the mechanism of the reaction process, the following experiments were performed. The reaction of aryl methyl ketone **1a** (1.0 mmol) with I_2 (1.1 mmol) and CuO (1.1 mmol) was refluxed for 1.0 h in MeOH, and α-iodo ketone **1aa** was obtained in 96% yield (Scheme 4 (a)).[10] When aryl methyl ketone **1a** (1.0 mmol) was heated with I_2 (1.5 mmol) in DMSO at 95 °C, the substrate could be transformed to phenylglyoxal (**1ab**) or hydrated hemiacetal (**1ac**) in quantitative conversion (Scheme 4 (b)). Substrates **1aa** (1.0 mmol) and **2a** (2.0 mmol) were treated with I_2 (1.0 mmol) at 95 °C in DMSO, and the desired product **3aa** was obtained in 85% yield. This reaction of **1ac** and **2a** was treated with iodide (1.0 mmol) in DMSO at 95 °C, and the product **3aa** was obtained in excellent yield (>95%). This result clearly confirmed the intermediacy of phenacyl iodine **1aa** and phenylglyoxal **1ab** in the transformation.

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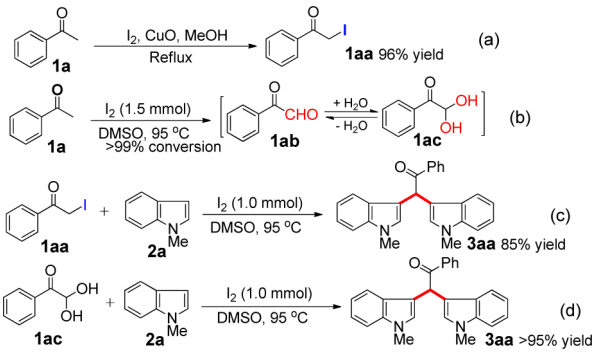
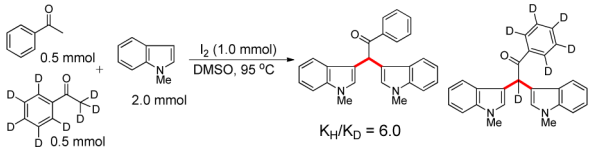
Scheme 4. Control Experiments



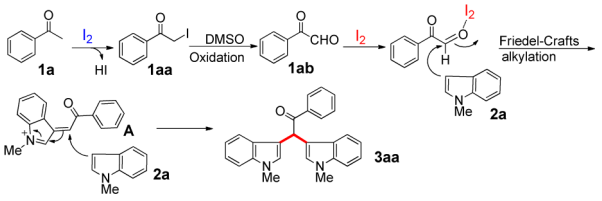
The intermolecular kinetic isotope (KIE) was also measured through a competition process of **2a** with a mixture of **1a** and **1a**-d_8 (1:1) (**1a**-d_8, D > 95%) in the presence of I_2 in DMSO at 95 °C (Scheme 5). The relative rate constant of K_H/K_D was determined to be 6.0. The result indicates that C−H bond cleavage of CH_3 in aryl methyl ketone **1a** is involved the rate-determining step (RDS) during the domino process.

Scheme 5. Intermolecular Kinetic Isotope Experiment



On the basis of the above results, a possible mechanism of the present reaction was proposed using acetophenone (**1a**) and *N*-methylindole (**2a**) as an example (Scheme 6). Initially, the substrate acetophenone **1a** reacted with I_2 to afford the intermediate α-iodo ketone **1aa**, Subsequently, intermediate **1aa** convergented to phenylglyoxal (**1ab**) by way of Kornblum oxidation in the presence of DMSO.[11] The aldehyde group of phenylglyoxal (**1ab**) was activated by excess or regenerated Lewis acid I_2.[12] Then, *N*-methylindole **2a** could attack the activated aldehyde group of phenylglyoxal (**1ab**) to give the 3-alkylidene-3*H*-indolium cation **A**. Finally, another *N*-methylindole **2a** could further trap the cation **A** to give the desired product **3aa**.

Scheme 6. Proposed Mechanism



In conclusion, we developed a molecular I_2-promoted sp^3 C−H bond dual-(het)arylation protocol for the synthesis of 2,2-bisindolyl-1-arylethanones from simple and readily available aryl methyl ketones and indole derivatives. In the transformation, three mechanism-different reactions (iodination, Kornblum oxidation, and Friedel−Crafts alkylation) were assembled in a single reactor. It is notable that the reaction performs well in the absence of any metal, base, or ligand. Because of the above-mentioned characteristics of this reaction, it should be of great utility in organic chemistry. Further studies on the applications of this strategy will be reported in due course.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant 21032001) and PCSIRT (No. IRT0953). We also thank Dr. Chuanqi Zhou, Hebei University, for analytical support.

Supporting Information Available. Spectrascopic data and general procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.