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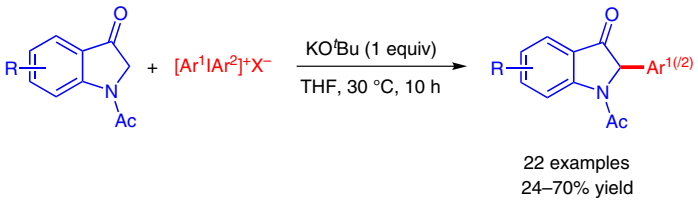
tert-Butoxide-Mediated Arylation of 1-Acetylindolin-3-ones with Diaryliodonium Salts

Yanxia Zhang[a,b]
Jianwei Han*[b]
Zhen-Jiang Liu*[a]

[a] School of Chemical and Environmental Engineering, Shanghai Institute of Technology, 100 Haiquan Road, Shanghai 201418, P. R. of China
zjliu@sit.edu.cn
[b] Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 345 Ling Ling Road, Shanghai 200032, P. R. of China
jianweihan@sioc.ac.cn



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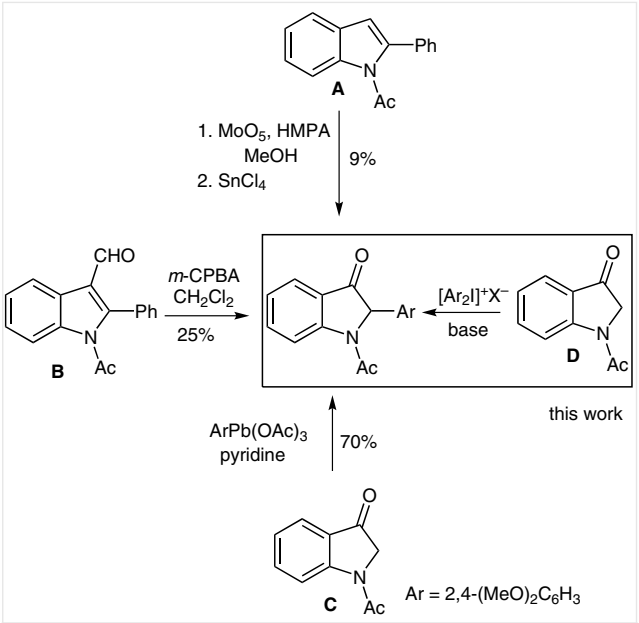
Abstract A procedure for the 2-arylations of indolinone derivatives with diaryliodonium salts mediated by potassium *tert*-butoxide is developed. Various monoarylated indolinone derivatives are readily obtained in 24–70% yield via this method. The alkylation of monoarylated indolinone derivatives with allyl bromide or benzyl bromide affords the corresponding 2,3-disubstituted products in 60% and 70% yield, respectively.

Key words arylation, diaryliodonium salts, metal-free, indolinone, alkylation

Arylations under transition-metal-free conditions have recently attracted significant attention due to the drawbacks of toxicity, cost and pollution problems associated with organometallic chemistry.[1] Iodine(III) reagents such as diaryliodonium salts possess similar properties to those of transition-metal-complexes, and hence can be employed as alternative metal-free reactants in reaction pathways that typically require heavy-metal reagents.[2] For example, aryl–metal reagents such as Ar_4Sn, $Ar_2Pb(OAc)_2$, Ar_3Bi, Ar_2TlCl, $ArB(OH)_2$ and so on, are efficient arylating agents. Similarly, a diaryliodonium salt can transfer one of its aryl groups to various nucleophiles to furnish arylated products, this being a result of their highly electron-deficient nature and the excellent leaving ability of the aryl iodide.[2,3] As such, several methods for C-, N-, O- and S-arylations using diaryliodonium salts as arylating reagents have been reported by several research groups.[3] Most of the recent developments in C-arylations have focused on coupling reactions of aromatic nucleophiles such as electron-rich aromatic heterocycles and naphthalene.[4]

Although C(sp^3)-arylations of carbonyl compounds using hypervalent iodonium salts were reported in the early 1960s,[5] interest in simple, mild and metal-free arylations with other valuable nucleophiles has experienced a renaissance in recent years.[6] Manetsch reported a metal-free arylation of ethyl acetoacetate for the synthesis of 3-aryl-4(1*H*)-quinolones.[7] Furthermore, a mild protocol for the C-4 arylation of 4-substituted pyrazolin-5-ones with diaryliodonium salts promoted by 4-(*N*,*N*-dimethylamino)pyridine (DMAP) has been described.[8] On the other hand, the indolinone moiety is found frequently in a wide-spectrum of naturally occurring bioactive products and compounds of pharmaceutical interest. 2-Arylated indolin-3-ones have been used as important building blocks for further synthetic transformations.[9] However, the reported approach for the preparation of 2-arylated indolinones is via Baeyer–Villiger oxidation of indole derivatives which are substituted with a phenyl group at C-3 (Scheme 1, **A** and **B**). Obviously, this method is restricted by the limited number of available substrates.[10] In 1992, Mérour and Finet reported a brief method for the direct arylation of indolin-3-ones with aryllead triacetates, but only electron-rich polymethoxyphenyllead reagents could be employed in the reaction (Scheme 1, **C**).[11] To the best of our knowledge, direct metal-free arylations at position C-2 of indolin-3-ones, with a wide reaction scope, remains unexplored. Herein, we present a *tert*-butoxide-mediated arylation of indolin-3-ones using diaryliodonium(III) salts to provide access to diverse 2-arylindolin-3-ones (Scheme 1, **D**).

Our investigation commenced with a set of experiments to evaluate the arylation of 1-acetylindolin-3-one (**1a**), in which the 1-acetyl protecting group is essential for its stabilization, with diphenyliodonium triflate (**2a**) in order to optimize the reaction conditions (Table 1). Initially, we examined a range of bases and solvents at 30 °C. It was found that the desired monoarylated product **3aa** could be obtained in 58% yield together with small amounts of the diarylated product **4** (Figure 1) when using one equivalent of



Scheme 1 Different approaches toward the synthesis of 2-arylated indolinones

potassium *tert*-butoxide (*t*-BuOK) as the promoter and tetrahydrofuran as the solvent. Other alkali bases such as potassium hydroxide (KOH), potassium carbonate (K_2CO_3), sodium methoxide (NaOMe), and sodium hexamethyldisilazide (NaHMDS) gave **3aa** in slightly lower yields of 30–45% under similar conditions (Table 1, entries 1–5).

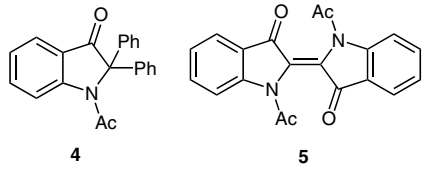
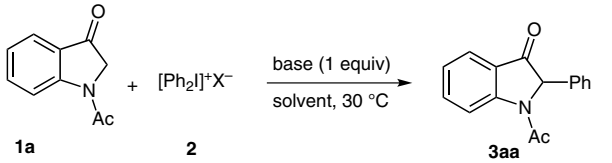


Figure 1 Byproducts **4** and **5**

A range of organic bases including triethylamine (Et_3N), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-(*N*,*N*-dimethylamino)pyridine and Proton-sponge were screened, with the results showing that the strong bases 1,8-diazabicyclo[5.4.0]undec-7-ene and Proton-sponge were effective in the reaction, while almost no conversion was observed in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine in tetrahydrofuran as the solvent after 10 hours (Table 1, entries 6–9).

Next, a solvent screen revealed that the conversion into **3aa** was also efficient in methanol and dichloromethane (Table 1, entries 10–13). However, a purple dye (**5**; Figure 1) was also isolated, apparently via dimerization of **1a** in dichloromethane. Furthermore, an evaluation of the anions of

Table 1 Optimization of the Reaction Conditions for the Arylation of Indolinones[a]



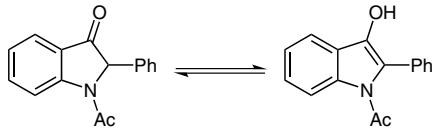
Entry	Base	X⁻	Solvent	Yield (%)[b]
1	*t*-BuOK	OTf	THF	58
2	KOH	OTf	THF	45
3	K_2CO_3	OTf	THF	41
4	NaOMe	OTf	THF	30
5	NaHMDS	OTf	THF	35
6	Proton-sponge	OTf	THF	43
7	DBU	OTf	THF	43
8	DMAP	OTf	THF	trace
9	Et_3N	OTf	THF	trace
10	*t*-BuOK	OTf	MeOH	56
11	*t*-BuOK	OTf	toluene	37
12[c]	*t*-BuOK	OTf	CH_2Cl_2	50
13	*t*-BuOK	OTf	*t*-BuOH	trace
14	*t*-BuOK	OTs	THF	58
15	*t*-BuOK	BF_4	THF	55
16	*t*-BuOK	PF_6	THF	61
17	*t*-BuOK	Br	THF	57
18[d]	*t*-BuOK	OTf	THF	60

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.2 mmol, 1.0 equiv), base (0.2 mmol, 1.0 equiv), solvent (2 mL), 30 °C, 10 h; unless otherwise specified.
[b] Yield of isolated product.
[c] Organic dye **5** was isolated.
[d] Freshly sublimated *t*-BuOK was employed.

the diphenyliodonium species showed that the nature of the counteranion did not have a significant influence on the yield of the desired product (Table 1, entries 14–17).

It is worth noting that enol–keto tautomerism of **3aa** to give an equilibrium mixture with **3aa′** was observed by ^1H NMR spectroscopy after a solution of **3aa** had been allowed to stand for a couple of hours (Scheme 2). The instability of **3aa** might be the reason behind the generally low yields of this arylation reaction. Furthermore, these findings also hampered our initial target of achieving asymmetric monoarylations of 1-acetylindolin-3-ones.

With optimized conditions in hand, we subsequently examined the structural diversity of various iodonium salts as coupling partners in the arylation of 1-acetylindolin-3-one. As shown in Table 2, a wide variety of functionalities with diverse electronic nature, such as electron-donating methoxy and electron-withdrawing nitro groups on the ar-

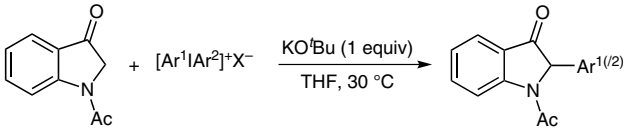


3aa 3aa'

Scheme 2 Enol–keto tautomerism of **3aa** to give an equilibrium mixture with **3aa**′

omatic ring, were tolerated (Table 2, entries 1–10). However, steric factors severely affected the reactivity: almost no reaction took place with bis-(2,4,6-trimethyldiphenyl)iodonium triflate as the arylating reagent (Table 2, entry 11). When $[(2\text{-thienyl})_2]$I]OTs was employed under the standard conditions, the heterocyclic thiophene ring was unfortunately not transferred to furnish the desired product (**3am**).

Table 2 Scope of the Iodonium Salts in the Arylation of Indolinone **1a**[a]



1a 2 3

Entry	Ar^1	Ar^2	X^-	Product	Yield (%)[b]
1	4-MeC_6H_4	4-MeC_6H_4	OTf	**3ab**	41
2	4-FC_6H_4	4-FC_6H_4	OTf	**3ac**	36
3	4-ClC_6H_4	4-ClC_6H_4	OTf	**3ad**	37
4	4-BrC_6H_4	4-BrC_6H_4	OTf	**3ae**	41
5	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	OTf	**3af**	40
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	OTf	**3ag**	27
7	2-MeC_6H_4	2-MeC_6H_4	OTf	**3ah**	55
8	3-MeC_6H_4	3-MeC_6H_4	OTf	**3ai**	57
9	3-FC_6H_4	3-FC_6H_4	OTf	**3aj**	26
10	3-$O_2NC_6H_4$	3-$O_2NC_6H_4$	PF_6	**3ak**	50
11	mesityl	mesityl	OTf	**3al**	trace
12	2-thienyl	2-thienyl	OTs	**3am**	trace
13	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	OTf	**3an**/**3ag**	46:0
14	4-ClC_6H_4	mesityl	OTf	**3ad**/**3al**	5:10
15	4-BrC_6H_4	mesityl	OTf	**3ae**/**3al**	12:17
16	4-MeC_6H_4	mesityl	OTf	**3ab**/**3al**	12:21
17	3-MeC_6H_4	mesityl	OTf	**3ai**/**3al**	6:10

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol, 1.0 equiv), *t*-BuOK (0.2 mmol, 1.0 equiv), THF (2 mL), 30 °C, 10 h.
[b] Yield of isolated product.

In connection with the influence of the electronic properties on the ability to transfer different aromatic rings, unsymmetric 4-methoxy-4′-nitrodiphenyliodonium (**2n**) was used in the reaction. It was interesting to find that 2-nitrophenyl product **3an** was isolated exclusively in 46% yield (Table 2, entry 13). Unsymmetric [ArI(mesityl)]OTf transferred both the aryl and mesityl groups to give mixtures of products in different ratios (Table 2, entries 14–17). Notably, in each case, mesitylated indolinone **3al** was obtained as the major product.

To further probe the scope of this reaction, a range of substituted 1-acetylindolin-3-ones was phenylated under the standard conditions with diphenyliodonium triflate (Table 3). Generally, the conditions proved to be effective for a variety of 1-acetylindolin-3-one derivatives bearing different substituents on the indolinone skeleton. Substituents including halogens, methyl and methoxy groups on each position of the benzene ring of the indolinone framework were tolerated. The reactions gave the corresponding phenylated products **3ba**–**ja** in good yields ranging from 24–70%.

To illustrate the scope for the potential utility of this reaction, monosubstituted 1-acetyl-indolin-3-ones **4a**,**b** were phenylated with diphenyliodonium triflate (**2a**) to generate products **5a**,**b**, which possess quaternary carbon centers, in quantitative yields (Scheme 3, eq. 1). Moreover, we performed the vinylation and alkynylation of 1-acetylindolin-3-one (**1a**) using iodonium salts **6** under the standard conditions; only disubstituted products **7a** and **7b** were afforded in 23% and 45% yield, respectively (Scheme 3, eq. 2). Inspired by these results, a final set of investigations focused on further transformation of mono-2-phenylated indolin-3-one (**3aa**) was carried out. Specifically, we attempted the alkylation of **3aa** with allyl bromide and benzyl bromide, and pleasingly found that these reactions under the optimized conditions provided alkylated products **9a** and **5b** in 60% and 70% yield, respectively (Scheme 3, eq. 3).

In summary, we have developed a method for the 2-arylation of indolinone derivatives with diaryliodonium salts. The procedure is tolerant of a variety of substituents, and various monoarylated indolinones can be readily obtained via this protocol.[12] Moreover, the further transformation of monoarylated indolinone derivatives with various electrophiles has been demonstrated, which could provide an access to bioactive compounds bearing the 2-arylated indolinone core.

Acknowledgment

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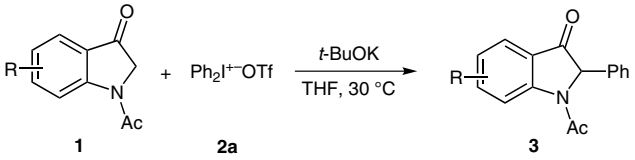
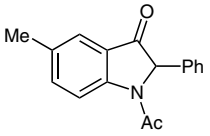
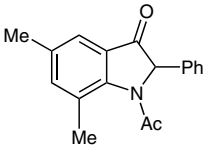
Table 3 Phenylation of Different Indolinone Derivatives under the Optimized Reaction Conditions[a,b]



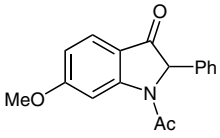
1 **2a** **3**



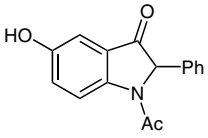
3ba, 37%



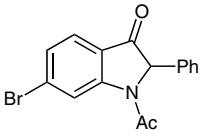
3ca, 47%



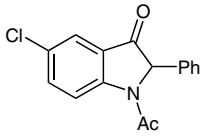
3da, 60%



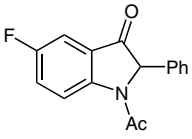
3ea, 24%



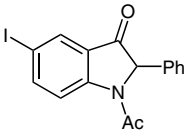
3fa, 70%



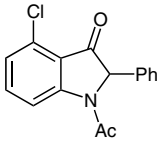
3ga, 57%



3ha, 52%

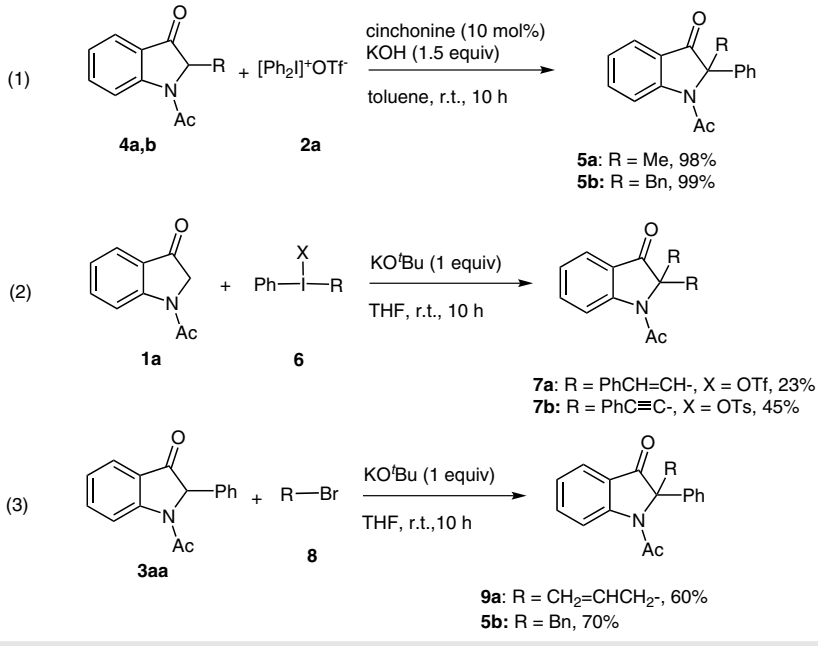


3ia, 48%



3ja, 59%

[a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), *t*-BuOK (0.2 mmol, 1.0 equiv), THF (2 mL), 30 °C, 10 h.
[b] Yields are those of isolated products.



Scheme 3 Related transformations with indolinone derivatives

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560575.

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(12) **Compounds 3ba–ja; General Procedure**

Indolinone **1** (0.2 mmol, 1 equiv) and *t*-BuOK (22.4 mg, 0.2 mmol, 1.0 equiv) were added to a Schlenk tube. THF (2 mL) was added using a syringe and the mixture was stirred for 15 min. Next, iodonium salt **2** (0.0860 g, 0.2 mmol, 1.0 equiv) was added and the mixture was stirred at 30 °C for 10 h. After cooling to r.t., the solvent was removed in vacuo and the residue was purified over silica gel (EtOAc–hexane) to afford the desired product. Analytical data for representative sample **3aa** is provided below.

1-Acetyl-2-phenylindolin-3-one (3aa)

Yield: 29.2 mg (58%); white solid; mp 125–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 7.8 Hz, 1 H), 7.80–7.65 (m, 2 H), 7.44–7.32 (m, 3 H), 7.30–7.22 (m, 3 H), 5.19 (s, 1 H), 2.05 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.2, 169.5, 154.1, 137.8, 134.8, 129.7, 129.0, 126.0, 125.0, 123.0, 118.7, 107.9, 69.9, 24.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}NO_2$: 252.1025; found: 252.1025.