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Transition-Metal-Free Direct Arylation and Esterification Reaction of Unprotected Indolylcarboxylic Acid Derivatives: A New Entry to 2-(1*H*-Indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazoles and Aryl 1*H*-Indole-2-carboxylates

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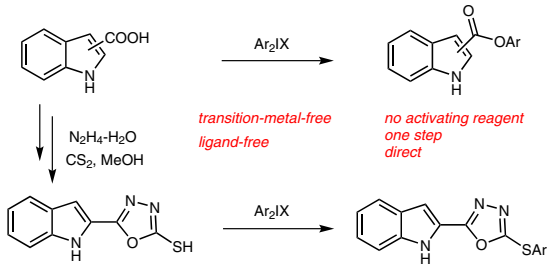

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Abstract An efficient, ligand-free, transition-metal-free, direct arylation and esterification reaction of unprotected indolylcarboxylic acid derivatives with diaryliodonium salts was developed, thus providing a new entry to 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole and aryl 1*H*-indole-2-carboxylate derivatives with good yields.

Keywords arylation, diaryliodonium salts, indolylcarboxylic acids, esterification, transition-metal-free

Aryl 1*H*-indole-2-carboxylate and 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole derivatives are important types of natural products and intermediates for pharmaceuticals, medicines, and pesticides (Figure 1).[1] Many scientists have already proved that aryl 1*H*-indole-2-carboxylate derivatives demonstrate benign biological activities, such as antilipid peroxide (LP) activity, antisuperoxide formation, and have been shown to function as antioxidants, antiovulatory antagonists of LHRH related to antide, X inhibitors, Xa inhibitors, FXa inhibitors, cholecystokinin antagonists, antiovulatory antagonists and anticoagulants, etc.[2] Moreover, these indole derivatives have also been applied as antibiotic, antiparasitic, antitumoral, antimycobacterial, and anti-inflammatory agents.[1h,3]

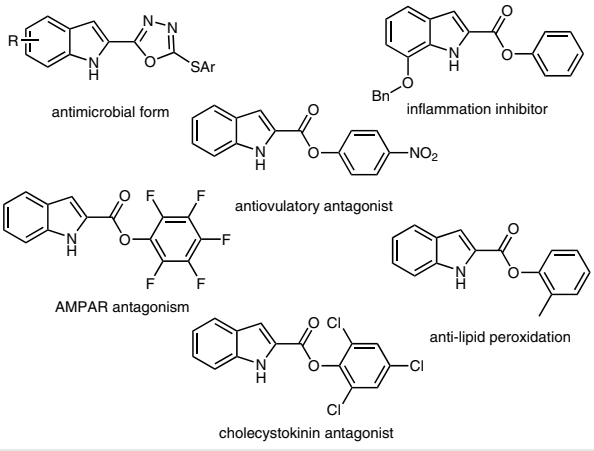
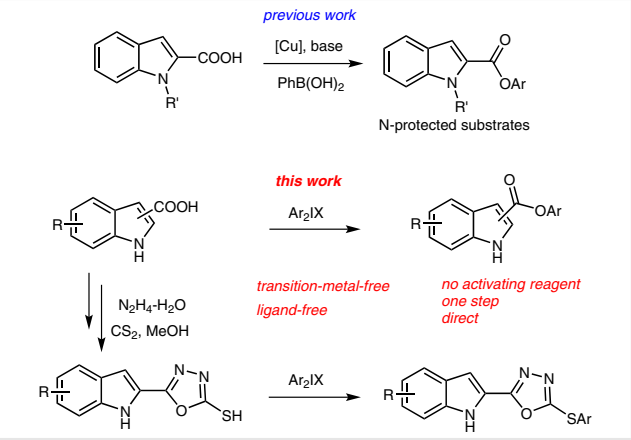


Figure 1 Biologically active 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole and aryl 1*H*-indole-2-carboxylate derivatives

During the past ten years, some chemists have investigated the synthesis of these aryl 1*H*-indole-2-carboxylate derivatives.[4] Generally, two main methods for the preparation of these indole derivatives have been developed: One is the two-step method, which uses thionyl chloride and 1,1′-carbonyldiimidazole (CDI) or oxalyl chloride as the activating reagent to elevate substrate activity;[5] the other is the transition-metal-catalyzed esterification reaction of indolylcarboxylic acids and arylboronic acids.[6] Recently, Mochizuki et al. used the first method to synthesize indole acyl chlorides under thionyl chloride conditions and converted these acyl chlorides into the corresponding aryl 1*H*-indole-2-carboxylate derivatives within two steps.[7] In 2011, Rossi and Martín converted carboxylic acids into amides using 1,1′-carbonyldiimidazole as activating reagent, then dealt with phenols to obtain aryl 1*H*-indole-2-carboxylate derivatives with a two-step method.[5a] In 2014, Baell and coworkers developed the synthesis of 3-amino-1*H*-indole-2-carboxylate through use of the cyclization method.[8] Recent-

ly, Liu and co-workers described copper-catalyzed direct O-arylation reactions of carboxylic acids with arylboronic acids under silver carbonate and DMSO conditions with moderate to good yields.[9]

Concurrently, many scientists found that diaryliodonium salts are very useful coupling reagents in the field of α-arylation reactions and C–H activation reactions.[10,11] Diaryliodonium salts have many advantages, like easy synthesis and high reactivity, among others.[12] Very recently, several groups have communicated their results in this area, including Olofsson,[13] Gaunt,[14] Greaney,[15] Shibata,[16] Chen,[17] Zhang and Yu,[18] Nagorny,[19] Chatani,[20] Manetsch,[21] Stuart,[22] and others.[23] Based on the coupling reactions of diaryliodonium salts in our group,[24a,b] herein, we reported a simple, efficient, ligand-free, transition-metal-free, direct esterification reaction of unprotected indolylcarboxylic acids and diaryliodonium salts, which provides a new method for the synthesis of aryl 1*H*-indole-2-carboxylate derivatives with good yields (Scheme 1).



Scheme 1 The synthesis of 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole and aryl 1*H*-indole-2-carboxylate derivatives

To begin this projection, the simple 1*H*-indole-2-carboxylic acid (**1a**) was chosen to react with diphenyliodonium triflate (**2a**) under various reaction conditions (Table 1). First, we selected toluene as the solvent and KOH as the base. To our delight, we found that the desired product was separated with moderate yield (Table 1, entry 1). Secondly, the blank test showed that the base played an important role in this reaction, so various bases were checked. The results showed that K_2CO_3 was better than other bases (Table 1, entry 4). Next, the evaluation of a range of solvents on the activity was carried out (Table 1, entries 9–15). The results showed that toluene was superior to other solvents.

Having established the optimal conditions for the reaction of 1*H*-indole-2-carboxylic acid with diphenyliodonium triflate to obtain aryl 1*H*-indole-2-carboxylate derivatives, we explored the reaction scope, and the results are summarized in Table 2. In general, all the 1*H*-indole-2-carboxylic

Table 1 Screening of Reaction Conditions[a]

Entry	Base	Solvent	Yield (%)[b]
1	KOH	toluene	60
2	Cs_2CO_3	toluene	71
3	K_3PO_4	toluene	59
4	K_2CO_3	toluene	84
5	Et_3N	toluene	<5
6	none	toluene	<5
7	*t*-BuOK	toluene	37
8	AcOH	toluene	<5
9	K_2CO_3	EtOH	<5
10	K_2CO_3	THF	<5
11	K_2CO_3	CH_2Cl_2	19
12	K_2CO_3	DMF	<5
13	K_2CO_3	xylene	21
14	K_2CO_3	DMSO	<5
15	K_2CO_3	DCE	14
16	K_2CO_3	toluene	79[c]

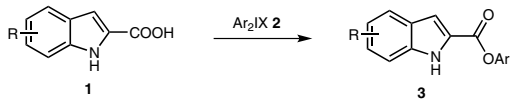
[a] Reaction conditions: 1*H*-indole-2-carboxylic acid (0.5 mmol), diphenyliodonium triflate (0.6 mmol), base (0.75 mmol), solvent (2 mL), 130 °C or reflux, 12 h.
[b] Isolated yield.
[c] Under N_2.

acids were converted completely to produce the corresponding products. The substrates having various electron-donating or electron-withdrawing goups, such as MeO, NO_2, F, and Br, can be tolerated in order to obtain the corresponding products with moderate to good yields in most cases. The highest yield was obtained in the case of 5-fluoro-1*H*-indole-2-carboxylic acid as substrate (Table 2, entry 3). When the anion was changed into BF_4 or OTs, the reaction gave slight lower yields (Table 2, entries 10–15). It should be noted that the reaction could not happen when bromide salt was used in this reaction (Table 2, entry 16).

Encouraged by such promising results, we applied the above methods to different substrates. The results are summarized in Figure 2. We were pleased to find that the corresponding products were obtained with moderate to good yields under the standard conditions. All kinds of the unprotected acids were smoothly converted into aryl ester derivatives.

It is well known that indole thiazoles belongs to a structural group in many natural products, which exhibit antifungal, antibacterial, anticancer, and antithrombotic activities.[1l,m] The preparation and synthesis of indole thiazoles have been a topic of special interest to medicinal and syn-

Table 2 Substrate Scope Experiments[a,b]



Entry	R	Ar	X	Yield (%)
1	H	Ph	OTf	**3a** 84
2	5-OMe	Ph	OTf	**3b** 79
3	5-F	Ph	OTf	**3c** 77
4	6-NO_2	Ph	OTf	**3d** 68
5	5-Br	Ph	OTf	**3e** 72
6	H	4-MeC_6H_4	OTf	**3f** 71
7	5-OMe	4-MeC_6H_4	OTf	**3g** 64
8	5-F	4-MeC_6H_4	OTf	**3h** 83
9	5-Br	4-MeC_6H_4	OTf	**3i** 68
10	H	4-MeC_6H_4	BF_4	**3f** 63
11	5-OMe	Ph	BF_4	**3b** 71
12	5-F	Ph	BF_4	**3c** 60
13	5-Br	4-MeC_6H_4	BF_4	**3i** 66
14	H	Ph	OTs	**3a** 70
15	5-OMe	4-MeC_6H_4	OTs	**3g** 62
16	H	Ph	Br	<5

[a] Reaction conditions: **1** (0.5 mmol), Ar_2IX (0.6 mmol), K_2CO_3 (0.75 mmol), toluene (2 mL), 130 °C, 12 h.
[b] Isolated yield.

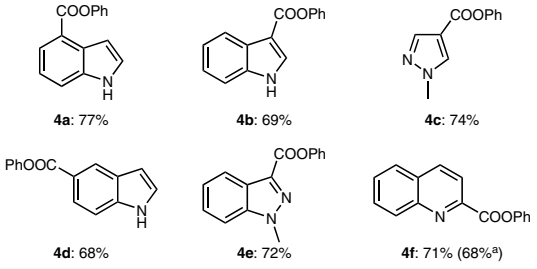
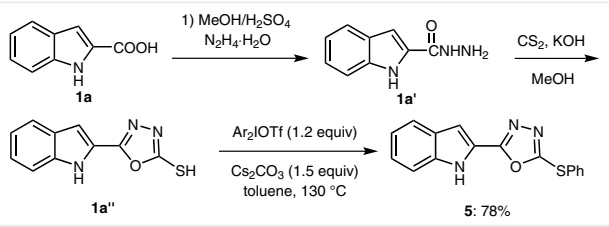


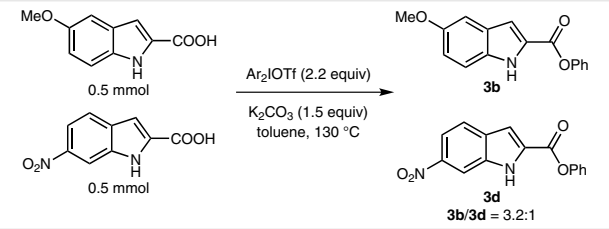
Figure 2 Substrate scope expansion experiment. *Reagents and conditions*: **1** (0.5 mmol), Ar_2IX (0.6 mmol), K_2CO_3 (0.75 mmol), toluene (2 mL), 130 °C, 12 h. Isolated yields are reported. [a] Under N_2.

thetic chemists. 5-(1*H*-indol-2-yl)-1,3,4-oxadiazole-2-thiol and 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole derivatives are the typical examples. Here, we found that 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole (**5**) was easily synthesized with diaryliodonium salts through this methodology with moderate yield (Scheme 2).



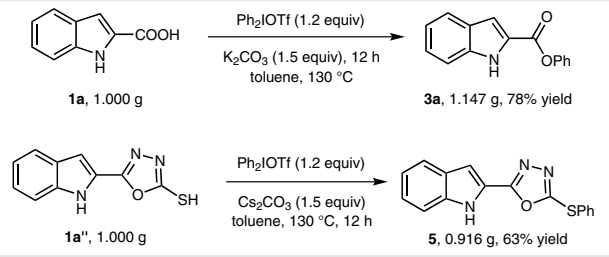
Scheme 2 The synthesis of 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole (**5**)

To elaborate on this reaction, competition experiments between 1*H*-indole-2-carboxylate derivatives with electron-withdrawing and electron-donating groups were set up. The results revealed that the reaction for 1*H*-indole-2-carboxylate with an electron-donating group is much better than for that with an electron-withdrawing group (Scheme 3).



Scheme 3 Intermolecular competition experiment of this esterification reaction

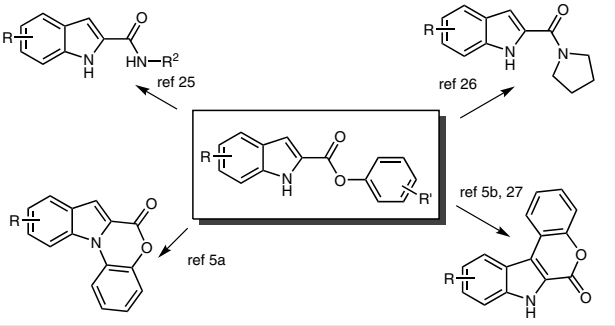
Because these aryl 1*H*-indole-2-carboxylate and 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole derivatives demonstrated good biological activity, the evaluation of this new method in a large-scale synthesis is necessary. Next, we performed this direct esterification reaction of unprotected indolylcarboxylic acids and diaryliodonium salts in a gram scale, good yield of the desired product **3a** was separated in 78% yield, while only moderate yield of 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole (**5**) was achieved (Scheme 4).



Scheme 4 The synthesis of phenyl 1*H*-indole-2-carboxylate (**3a**) and 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole (**5**) on a gram scale

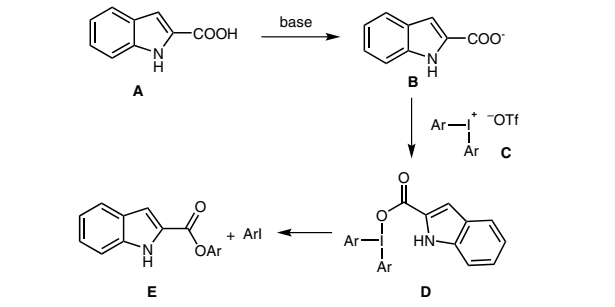
This methodology of direct esterification reaction of unprotected indolylcarboxylic acids and diaryliodonium salts provides a convenient route to synthesize aryl 1*H*-indole-2-

carboxylate derivatives. Besides their own biological performance and activity (Scheme 5), these compounds could be easily converted into *N*-phenyl-1*H*-indole-2-carboxamides,[25] (1*H*-indol-2-yl)(pyrrolidin-1-yl)methanones,[26] 6*H*-benzo[5,6][1,4]oxazino[4,3-*a*]indol-6-ones,[5a] and chromeno[3,4-*b*]indol-6(7*H*)-ones[5b,27] through the use of one or two steps.



Scheme 5 The transformations of aryl 1*H*-indole-2-carboxylate derivatives

Finally, a possible mechanism for the esterification reaction of unprotected indolylcarboxylic acids and diaryliodonium salts was proposed (Scheme 6). Initially, we proposed that 1*H*-indole-2-carboxylate was dealt with base and converted into 1*H*-indole-2-carboxylate ion, and subsequent exchange with diaryliodonium salts to form a T-shaped $Ar_2IOOCAr$ **D** intermediate.[28] Subsequent to the release of ArI as a byproduct, the product **E** was obtained to finish the reaction.



Scheme 6 The proposed possible mechanism

In summary, we developed efficient, ligand-free, transition-metal-free, direct S-arylation and esterification reactions of unprotected indolylcarboxylic acids and diaryliodonium salts with moderate to good yields. This provides a new method for the synthesis of aryl 2-(1*H*-indol-2-yl)-5-(phenylthio)-1,3,4-oxadiazole and aryl 1*H*-indole-2-carboxylate derivatives.[29]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562526.

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(29) **Typical Procedure for the Synthesis of 3a**

Ph_2IOTf (0.6 mmol) and toluene (2 mL) were stirred in a Schlenk tube at room temperature for a moment. Subsequently, 1*H*-indole-2-carboxylic acid (**1a**, 0.5 mmol) and K_2CO_3 (0.75 mmol) was added. The mixture was heated under 130 °C for 12 h and then cooled to room temperature. The resulting solution was directly purified by column chromatography with PE–EtOAc (5:1) as eluent to give phenyl 1*H*-indene-2-carboxylate (**3a**) as a yellow solid in 84% yield. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.48 (d, *J* = 8.2 Hz, 3 H), 7.39–7.33 (m, 3 H), 7.31–7.26 (m, 2 H), 7.21 (m, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.77, 150.45, 137.42, 129.56, 127.37, 126.31, 126.10, 125.88, 122.77, 121.71, 121.01, 112.12, 110.27.