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Palladium-catalyzed arylation/cyclization/desulfonation cascades toward 4-aryl quinolin-2(1*H*)-ones with diaryliodonium salts

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ABSTRACT

Palladium-catalyzed cascades of arylation/cyclization/desulfonation of *ortho*-aminocinnamate esters by using diaryliodonium salts afforded a wide range of 4-aryl quinolin-2(1*H*)-ones. As such, the desired 4-aryl quinolin-2(1*H*)-ones with potential biological activity has been synthesized in the yields of 34–96%.

Introduction

4-Aryl quinolin-2(1*H*)-ones are valuable class of biologically active substances in pharmaceutical research, such as HBV inhibitor (**A**, Fig. 1), Viridicatin (**B**, Fig. 1), Tipifamib (**C**, Fig. 1) and an efficient maxi-K opener (**D**, Fig. 1) to elicit penile erection with a novel mechanism for the treatment of male erectile function.[1] In light of their synthesis, various synthetic methods towards 4-aryl quinolin-2(1*H*)-ones were documented.[2] The condensation of 2-acetamidobenzaldehydes, the cyclization of cinnamanilides or *N*-aryl amides of 3-arylpropynoic acids under the action of strong acids or transition-metal catalysts have been developed to access 4-aryl 2-quinolinone structural motifs.[3] Noteworthy reports are transition-metal catalyzed cyclization of cascades, which provided a more efficient and practical route.[4]

Recently, diaryliodonium salts ($Ar_2I^+X^-$) were well studied in the electrophilic arylations due to their excellent reactivity.[5] By using $Ar_2I^+X^-$, we reported in 2015 that arylation/cyclization of *ortho*-hydroxylcinnamates by palladium catalysis afforded 4-arylcoumarin derivatives in good yields.[6] In a similar pattern, (*E*)-ethyl 3-(2-aminophenyl)-acrylate was also employed in this protocol; however, only nitrogen-arylated product was furnished without cyclization to give 4-arylquinolinone (**1**, Scheme 1). Of note, concurrently Kumar and co-workers reported a microwave-assisted oxygen-arylation of quinolones with diaryliodonium salts in the presence of a base, aryloxyquinolines were furnished in good yields (**2**, Scheme 1).[7]

In principle, diaryliodonium salts were tended to oxyphilic arylations or *N*-arylations of arylamines under a basic reaction medium.[5] We reasoned that modification of amine group of ethyl 3-(2-aminophenyl)-acrylate to reduce the basicity of arylamine by using a tosyl group, in which the reactivity of ArNHTs was allowed to undergo the cyclization process without *N*-arylative attack, therefore producing 4-aryl quinolin-2(1*H*)-ones (**3**, Scheme 1). Herein, we reported in detail the cascades of arylation/cyclization/desulfonation in the presence of palladium catalysts by using diaryliodonium salts.

Results and discussion

At the outset of the study, palladium-catalyzed arylative cyclization cascade of ethyl (*E*)-3-(2-((4-methylphenyl) sulfonamido)phenyl)acrylate **1a** with diphenyliodonium triflate **2a** was investigated as a model reaction (Table 1). According to the conditions of our previous arylation/cyclization of cinnamate ester,[6] the procedure also used DMF (dimethylformamide) as solvent in the presence of 10 mol% $Pd(OAc)_2$ as catalyst at 110 °C, it was pleased

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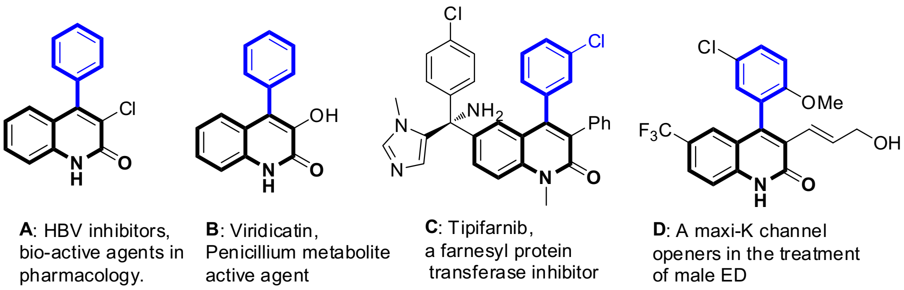
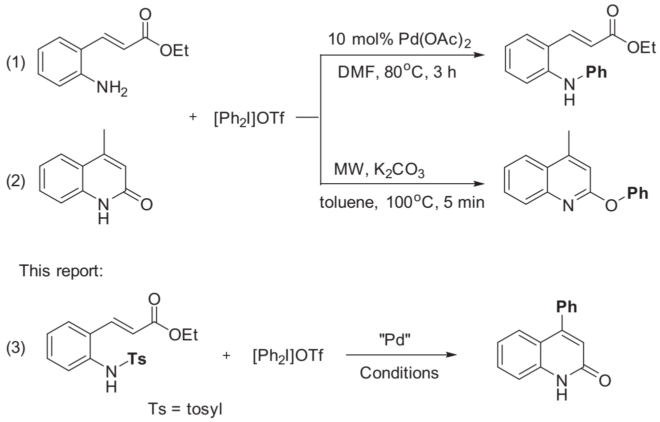


Fig. 1. Selective samples of 4-arylcoumarin derivatives.

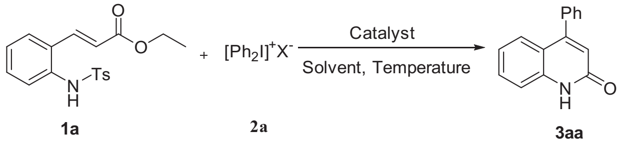


Scheme 1. Reactions towards 4-arylquinolines by using diaryliodonium salts.

to find that the desired product of **3a** was obtained in 81% yield (Table 1, entry 1). Interestingly, the tosyl group was cleaved off by a desulfonation reaction in one pot under the reaction conditions. The reaction does not work without palladium catalyst, and no product was observed by thin-layer chromatography when copper catalysts of CuI and $Cu(OTf)_2$ or nickel complex of $Ni(dppp)Cl_2$ as catalyst were employed in this reaction (Table 1, entries 2–5).

The evaluation of the activity of palladium catalysts showed that 5 mol% $Pd(PPh_3)_4$ gives the best yield of 93% (Table 1, entries 6–9). The examination of the solvent effect with experiments performed in dimethylsulfoxide, dichloroethane, *N*-methyl pyrrolidinone, acetonitrile, dioxane and *N*,*N*-dimethyl formamide suggested that DMF as solvent is the best choice (Table 1, entries 8 and 10–14). Reaction temperature and reaction time were also examined, the temperature of 120 °C and the reaction time of 12 h were found to be the optimal to give the highest yield of

Table 1
Screening of reaction conditions for synthesis of 4-aryl quinolin-2(1*H*)-ones.[a]



Entry	Cat.	Loading (mol%)	X^-	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	10	OTf	DMF	81
2	–	10	OTf	DMF	0
3	CuI	10	OTf	DMF	0
4	$Cu(OTf)_2$	10	OTf	DMF	0
5	$Cu(OAc)_2$	10	OTf	DMF	0
6	$PdCl_2$	10	OTf	DMF	88
7	$Pd(PPh_3)_4$	10	OTf	DMF	91
8	$Pd(PPh_3)_4$	5	OTf	DMF	93
9	$Pd(PPh_3)_4$	1	OTf	DMF	75
10	$Pd(PPh_3)_4$	5	OTf	DMSO	59
11	$Pd(PPh_3)_4$	5	OTf	DCE	0
12	$Pd(PPh_3)_4$	5	OTf	NMP	48
13	$Pd(PPh_3)_4$	5	OTf	Dioxane	Trace
14	$Pd(PPh_3)_4$	5	OTf	MeCN	Trace
15[c]	$Pd(PPh_3)_4$	5	OTf	DMF	96
16	$Pd(PPh_3)_4$	5	BF_4	DMF	90
17	$Pd(PPh_3)_4$	5	OTs	DMF	75
18	$Pd(PPh_3)_4$	5	PF_6	DMF	86
19	$Pd(PPh_3)_4$	5	Br	DMF	Trace
20[d]	$Pd(PPh_3)_4$	5	PhI	DMF	0

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst, and solvents (2 mL) at 110 °C for 12 h.
[b] Isolated yield.
[c] The reaction temperature was 120 °C.
[d] Iodobenzene was used in place of **2a**.