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Highly Regioselective α-Arylation of Coumarins *via* Palladium-Catalyzed C–H Activation/Desulfitative Coupling

Farnaz Jafarpour,[a,*] Mina Barzegar Amiri Olia,[a] and Hamideh Hazrati[a]

[a] School of Chemistry, College of Science, University of Tehran, 14155-6455 Tehran, Iran
Fax: (+98)-21-6649-5291; e-mail: jafarpur@khayam.ut.ac.ir

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Abstract: A novel regioselective α-arylation of coumarins with readily available arenesulfonyl chlorides and sodium arenesulfinates *via* palladium-catalyzed direct C–H functionalizations under mild reaction conditions is described. This protocol presents an unexpected and highly regio-controlled arylation of coumarins at C-3 to construct interesting 3-arylcoumarins with fascinating biological and fluorescent properties. The regioselectivity observed is in sharp contrast with that expected for the Heck reactions.

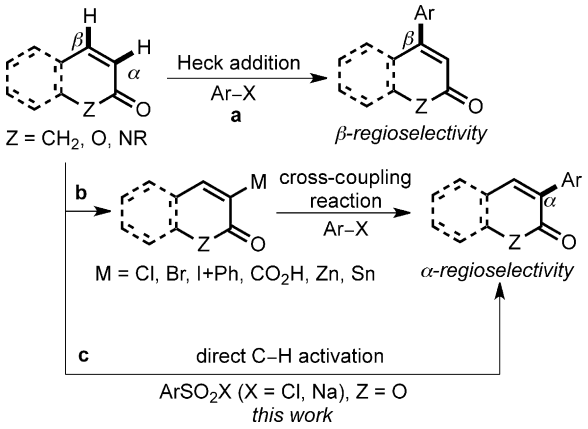
Keywords: α-arylation; 3-arylcoumarins; C–H activation; desulfitative arylation; palladium

Arylcoumarins have attracted considerable attention because of their extraordinary biological and pharmacological activities and their presence in a variety of natural products.[1] In addition, their applications in laser and dispersed fluorescent dyes, optical brighteners and emission layers (OLED) make this skeleton noteworthy.[2] Furthermore, these privileged structural motifs have been characterized as potent and selective monoamine oxidase inhibitors and are used in the treatment of neurological disorders such as depression, anxiety, Parkinson's and Alzheimer's diseases.[3]

Among various methods, transition metal-catalyzed cross-couplings such as Heck and Suzuki reactions have revolutionized C–C bond formation in synthetic strategies and functionalization of α,β-unsaturated carbonyl compounds as well.[4] It is well documented that in Heck-type reactions while electron-deficient olefins yield exclusively the β-arylated products[5] (Scheme 1, path **a**), electron-rich olefins generate a mixture of both α- and β-arylated ones.[6] Thus, the regioselectivity of the Heck reaction is the main point which must be considered in planning synthetic routes. Recently, we and other groups made some advances in the direct C-4 arylation of coumarins *via* the palladium-catalyzed oxidative Heck-type reaction of coumarins with arylboronic acids.[7] The strategy was further improved by Hong et al.[8] *via* a two-fold C–H activation of coumarins and simple arenes where the regioselectivity was reflected in a bias for C-4 arylation which is an expected regioselectivity in Heck reactions.[9]

α-Functionalization of unsaturated carbonyl compounds is a desirable but challenging strategy due to the requisite for prefunctionalizations at the α-position (Scheme 1, path **b**).[10] For instance, the Suzuki cross-coupling of arylboronic acids and 3-halocoumarins provides a route to 3-arylcoumarins which still needs prefunctionalization of the coumarins.[11] Very recently, we also reported a palladium-catalyzed decarboxylative arylation of coumarin-3-carboxylic acids using iodoarenes where the carboxylate group warranted regioselective arylation at C-3.[12]

To the best of our knowledge, despite the importance of direct α-arylation of α,β-unsaturated carbonyl compounds *via* C–H activation process only rare



Scheme 1. Transition metal-catalyzed arylation of α,β-unsaturated carbonyl compounds.

examples are reported which usually suffer from low functional group tolerance, low yields of adducts and harsh reaction conditions.[13]

Meanwhile, the recently increasing interest toward the use of inexpensive and readily available arenesulfonyl chlorides, hydrazides, acids and their sodium salts as potential aryl sources in transition metal cross-coupling reactions has become apparent.[14]

These thioorganic coupling partners can readily undergo C–S bond cleavage to liberate SO_2 under mild reaction conditions with no requisite for an *ortho*-electron-donating or -electron-withdrawing substitution (required in carboxylic acids). Very recently, these compounds have been successfully used as arylating agents in cross-coupling,[15] homo-coupling[16] and also Heck-type reactions where β-regioselectivity was given in all cases.[17,18]

In continuation of our interest in the direct arylation of heterocycles, herein we report our new findings that an α-regioselectivity in direct arylation of coumarins can be achieved by employing either arenesulfonyl chloride or sodium arenesulfinate coupling partners in the presence of catalytic amounts of palladium. This protocol allows for a waste minimized construction of biologically interesting 3-arylcoumarins in high yields using inexpensive sulfonyls or sulfinates and precluding prefunctionalization of coumarins. Regioselectivity, broad substrate scope and mild reaction conditions with no requisite for any ligands or bases are the advantages of the present work.

To achieve the purpose of desulfitative arylation of coumarins, first coumarin **1a** and *para*-toluenesulfonyl chloride **2a** were chosen as the model compounds and the reaction parameters (catalyst, solvent, base, etc.) were varied (Table 1). Our preliminary results revealed that palladium/PPh_3 catalytic systems with AgOAc as base in 1,4-dioxane were not effective and only traces of the desired product were obtained (entries 1–3). Screening reactions with respect to bases such as Cs_2CO_3, Na_2CO_3, K_2CO_3, $NaHCO_3$ and Ag_2CO_3 resulted in slightly increased yields (entries 4–6).

Applying conditions similar to Dong's work also did not provide satisfactory results (entry 7).[15m] Exploration of a variety of oxidants including copper, zinc, silver and persulfate salts proved $Cu(OAc)_2 \cdot H_2O$ as the most effective one where regioselective arylation of coumarin at C-3 was achieved in 62% yield (entries 8–18). Furthermore, it turned out that in the absence of any ligands, a comparable yield of the product was obtained and therefore, ligand-free conditions were established for later investigations (entry 19). Notably, base removal from the reaction conditions, even improved the yield further (entry 20). When other oxidants such as $ZnCl_2$ and AgOAc were subsequently explored under ligand- and base-free conditions, lower yields were obtained (entries 21 and 22).

Table 1. Optimization of desulfitative arylation of coumarin **1a**.[a]

Entry	[Pd]	[O]	L	Base	Yield [%]
1	$Pd(OAc)_2$		PPh_3	AgOAc	10
2	$PdCl_2$		PPh_3	AgOAc	12
3	$Pd(dba)_2$		PPh_3	AgOAc	0
4	$PdCl_2$		PPh_3	Cs_2CO_3	0
5	$PdCl_2$		PPh_3	K_2CO_3	0
6	$PdCl_2$		PPh_3	$NaHCO_3$	31
7[b]	$Pd(PhCN)_2Cl_2$	CuBr	PPh_3	Ag_2CO_3	32
8	$PdCl_2$	$Cu(OAc)_2$	PPh_3	$NaHCO_3$	62
9	$PdCl_2$	$CuCl_2$	PPh_3	$NaHCO_3$	40
10	$PdCl_2$	$CuSO_4$	PPh_3	$NaHCO_3$	38
11	$PdCl_2$	$ZnCl_2$	PPh_3	$NaHCO_3$	57
12	$PdCl_2$	$Zn(OAc)_2$	PPh_3	$NaHCO_3$	0
13	$PdCl_2$	ZnI_2	PPh_3	$NaHCO_3$	0
14	$PdCl_2$	Ag_2CO_3	PPh_3	$NaHCO_3$	0
15	$PdCl_2$	AgOAc	PPh_3	$NaHCO_3$	54
16	$PdCl_2$	Ag_2O	PPh_3	$NaHCO_3$	17
17	$PdCl_2$	$Na_2S_2O_8$	PPh_3	$NaHCO_3$	14
18	$PdCl_2$	$(NH_4)_2S_2O_8$	PPh_3	$NaHCO_3$	0
19[b]	$PdCl_2$	$Cu(OAc)_2$		$NaHCO_3$	67
20	**$PdCl_2$**	**$Cu(OAc)_2$**			**78**
21	$PdCl_2$	$ZnCl_2$			5
22	$PdCl_2$	AgOAc			58

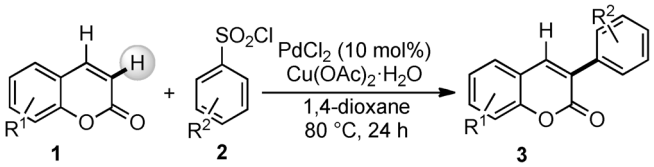
[a] *Reaction conditions:* *p*-toluenesulfonyl chloride **2a** (0.1 mmol, 1 equiv.), coumarin **1a** (0.3 mmol, 3 equiv.), Pd catalyst (10 mol%), oxidant (1 equiv.), ligand (20 mol%), base (2 equiv.), 4 Å MS in 1,4-dioxane (0.2 M) at 80 °C for 24 h.

[b] Base (1 equiv.) used.

We were pleased to find that the use of the $PdCl_2$/$Cu(OAc)_2$ in 1,4-dioxane provided the desired 3-arylcoumarin **3a** with high regioselectivity in 78% isolated yield. An excess amount of coumarin ensured the complete conversion of starting material to the desired 3-arylcoumarin and the excess of unreacted coumarin was recovered at the end of the reaction. It is noteworthy that the 4-arylated coumarin was not observed in the reaction mixture.

The scope of both starting materials compatible with the direct arylation reaction was next investigated. Accordingly, coumarins and arenesulfonyl chlorides with various electron-donating and electron-withdrawing groups (alkyl, alkoxy, hydroxy and nitro groups) were tested and a broad reaction scope was established (Table 2). Reaction of coumarin **1a** with arenesulfonyl chlorides possessing various steric and electronic properties resulted in good to high yields of 3-arylcoumarins (entries 1–4). More sterically encumbered naphthalenesulfonyl chloride **2e** underwent the desulfitative arylation reaction in a relatively lower yield (entry 5). 6-Methylcoumarin **1b** also afforded

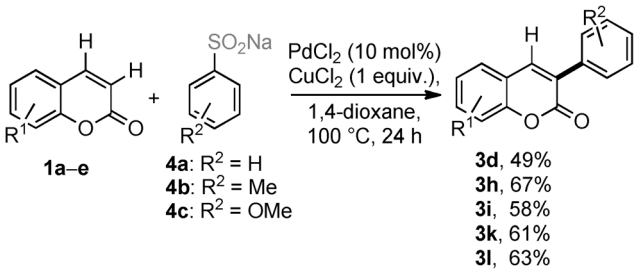
Table 2. Scope of regioselective desulfitative arylation of coumarins.[a]



Entry	R^1	R^2	Product	Yield [%]
1	H **1a**	4-CH_3 **2a**	**3a**	78 (72)[b]
2	H **1a**	4-OMe **2b**	**3b**	66
3	H **1a**	4-pentyl **2c**	**3c**	72
4	H **1a**	H **2d**	**3d**	68
5	H **1a**	2-naphthyl **2e**	**3e**	47
6	6-Me **1b**	4-$CH(CH_3)_2$ **2f**	**3f**	75
7	6-Me **1b**	2-naphthyl **2e**	**3g**	63
8	6-Me **1b**	4-CH_3 **2a**	**3h**	80
9	6-Me **1b**	H **2d**	**3i**	66
10	7-NEt_2 **1c**	H **2d**	**3j**	57
11	7-OEt **1d**	4-OMe **2b**	**3k**	64
12	6-OMe **1e**	H **2d**	**3l**	72
13	7-OMe **1f**	2-naphthyl **2e**	**3m**	65
14	7-OMe **1f**	4-CH_3 **2a**	**3n**	87
15	7-OH **1g**	H **2d**	**3o**	60
16	6-NO_2 **1h**	4-CH_3 **2a**	**3p**	traces

[a] All reactions were run under the optimized conditions.
[b] A 1.0 mmol scale was performed employing 5 mol% $PdCl_2$.

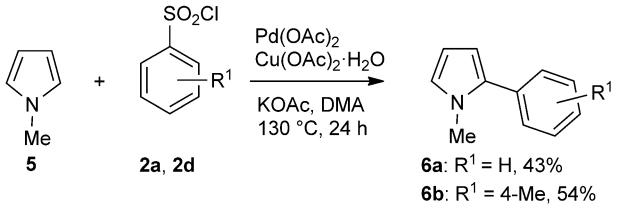
the desired products in high yields exceeding 63% (entries 6–9). This has significant synthetic utility based on interesting biological activities of 6-methyl-3-arylcoumarins.[3c] Next the scope of the reaction was explored with more electron-rich coumarins. Coumarins bearing amine and alkoxy groups also resulted in the corresponding arylcoumarins within a range of 57–87% isolated yields (entries 10–14). Gratifyingly, even sensitive functionalities such as hydroxy groups were also tolerated under the optimized reaction conditions and the reaction could be performed without protection of OH groups (entry 15).[19] Hydroxycoumarins have been proved to act as potent metal chelators, free radical scavengers and powerful chain-breaking antioxidants. They also show different cytotoxic values according to the positions of the OH groups in their structures.[20] We also investigated the reaction scope with electron-deficient coumarins with a nitro substituent. The corresponding arylated coumarin was obtained only in trace amounts under the optimized reaction conditions (entry 16). Furthermore, we sought to expand the scope of the reaction to include aliphatic sulfonyl chlorides. Unfortunately, benzyl- and methanesulfonyl chloride remained unreacted under the reaction conditions. Finally, we performed a 1.0-mmol scale experiment employing 5 mol% $PdCl_2$ which gratifyingly offered arylcoumarin **3a** in 72% isolated yield (Table 1, entry 1).



Scheme 2. Desulfitative arylation of coumarins with sodium arenesulfinates.

Motivated by these results, we next sought to expand the scope of regioselective direct arylation of coumarin at C-3 with arenesulfonyl chlorides to sodium sulfinates (Scheme 2). These compounds are more stable and moisture-insensitive compared to sulfonyl chlorides. Gratifyingly, the arylation reaction of coumarin **1a** with sodium benzenesulfinate **4a** under slightly altered reaction conditions afforded the desired 3-arylcoumarin **3d** albeit in moderate yield. Various coumarins arylated at C-3 were also obtained employing by alkyl- and alkoxy-substituted sodium sulfinates in yields ranging 58–67% (Scheme 2).

Additionally, continuing our efforts in the direct arylation of heterocycles[21] we turned our attention to apply this protocol to the important concept of the direct arylation of pyrroles. Although some focused efforts on regioselective desulfitative arylation of some fused heterocycles including indoles, benzoxazoles, thiazoles, imidazoles and 1,2,4-oxadiazoles with sodium sulfinates were reported,[15d,f,j–l] the direct arylation of pyrroles to the best of our knowledge is unprecedented. 2-Arylpyrroles have fascinating biological and pharmacological activities. For instance, analgesic and anti-inflammatory properties of these structural motifs are reported.[22] Additionally, 2-arylpyrroles are known to act as novel anticoccidial and antifungal agents.[23] In this regard, the reaction of *N*-methylpyrrole with sulfonyl chlorides **2a** and **2d** under some further optimized reaction conditions was explored and pleasingly regioselective arylation of pyrroles at C-2 was achieved in the presence of $Pd(OAc)_2/Cu(OAc)_2$ and addition of KOAc in DMA (Scheme 3). Further optimization and development of the scope of the reaction was then undertaken.



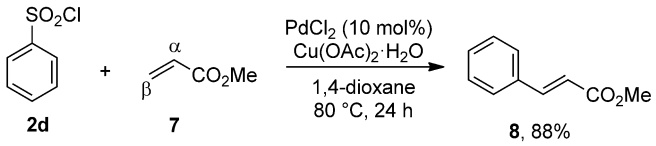
Scheme 3. Desulfitative arylation of pyrroles with arenesulfonyl chlorides.

Finally, the regioselectivity in desulfitative direct arylation of terminal alkenes under the optimized reaction conditions was examined. The results showed that with an acyclic electron-deficient alkene such as methyl acrylate, desulfitative arylation occurred exclusively at the least-substituted terminal β-position of the double bond (Scheme 4).[24]

Although the exact mechanism of this reaction is not clear, a possible pathway is proposed in Scheme 5. The first step is oxidative addition of palladium into S–Cl bond of arenesulfonyl chloride to generate intermediate **A** which goes a desulfitative process to form arylpalladium species **B**.[25] In the other cycle, C–H activation of coumarin generates intermediate **C**[26] which undergoes transmetallation[27] with **B** to produce diarylpalladium **D** followed by a reductive elimination process to afford the desired product.

Although the exact role of the copper salt is not clear, it was postulated that the copper salt can play the role of a palladium reoxidant and contribute in the desulfonation process to form the aryl metal species.[13a,28]

In summary, we have developed a novel, versatile, highly regioselective and step-economical desulfitative arylation of coumarins with arenesulfonyl chlorides and sodium sulfinates *via* a palladium catalytic system. The protocol exhibits a simple and new route to interesting 3-arylcoumarins that serve as the key intermediates in the synthesis of drug candidates and fluorescent dyes. The observed regioselectivity was reflected in a bias for arylation at C-3 instead of C-4 and in almost all cases 4-arylcoumarins were not observed. Furthermore, mild ligand- and base-free conditions were established in the desulfitative arylations using this arenesulfonyl chloride approach, which was not feasible in most of the previously reported α-arylation reactions. In addition, the scope was readily extended to the direct regioselective arylation of pyrroles leading to biologically interesting 2-arylpyrroles.



Scheme 4. Desulfitative arylation of methyl acrylate.

Experimental Section

Typical Experimental Procedure for Arylation of Coumarins with Arenesulfonyl Chlorides

A vial equipped with a stir bar was charged with toluenesulfonyl chloride (0.1 mmol, 1 equiv.), coumarin (3 equiv.), $PdCl_2$ (10 mol%), $Cu(OAc)_2$ (1 equiv.) and 4 Å MS. 1,4-Dioxane (0.2 M) was added and the vial was capped. The resulting mixture was heated in an oil bath at 80 °C for 24 h, cooled then filtered through a short plug of silica. Removal of the solvent gave a crude mixture which was purified by flash column chromatography (hexane/EtOAc gradient).

3-(4-Methylphenyl)-2*H*-chromen-2-one (3a): Yellowish solid; yield: 18 mg (78%); mp 160–162 °C (ref.[29] 161 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H), 7.58 (d, $J =$ 7.3 Hz, 2H), 7.49–7.44 (m, 2H), 7.29–7.22 (m, 2H), 7.22 (d, $J = 7.3$ Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 116.5, 119.9, 124.7, 128.0, 128.4, 128.5, 129.3, 129.8, 131.3, 132.0, 139.0, 139.4, 153.5, 160.9; anal. calcd. for $C_{16}H_{12}O_2$: C 81.34, H 5.12; found: C 81.65, H 5.26.

Acknowledgements

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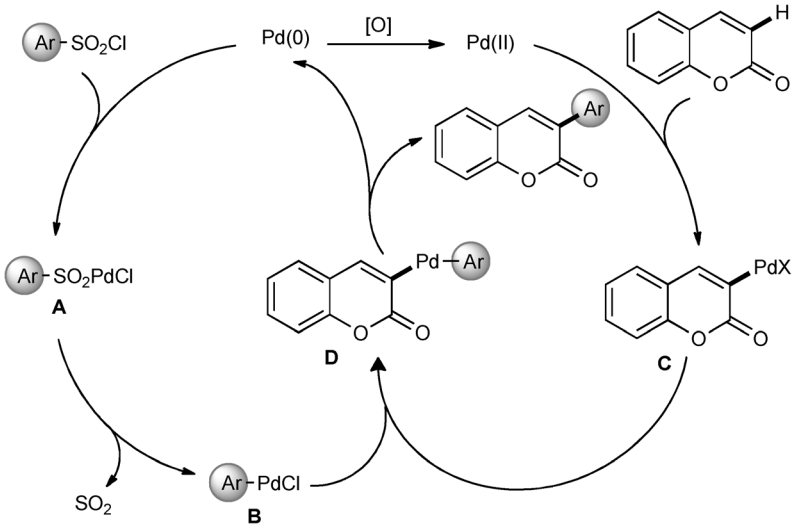

Scheme 5. A plausible mechanism for regioselective desulfitative arylation of coumarins.

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