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Regioselective Suzuki-Miyaura Cross-Coupling Reactions of the Bis(triflate) of 4,7-Dihydroxy-coumarin

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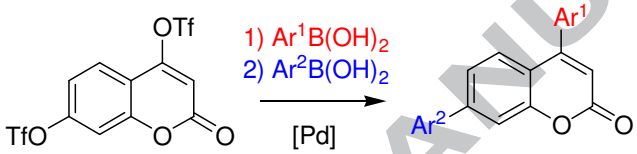

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ABSTRACT

Arylated coumarins were prepared by site-selective Suzuki-Miyaura cross-coupling reaction of the bis(triflate) of 4,7-dihydroxycoumarin. The reactions proceeded by initial attack to the sterically more hindered position, due to electronic reasons.

Neoflavones (4-arylcoumarins) are of considerable pharmacological relevance and occur in several natural products and synthetic drugs.[1] Natural and synthetic neoflavones have been reported to exhibit various kinds of pharmacological activities, such as anticancer,[2] antimalarial,[3] antibacterial,[4] antiprotozoal,[5] antivirus,[6] antidiabetic,[7] cytotoxic,[8] and anti-inflammatory activity.[9] Merck developed a 7-substituted 4-arylcoumarin as a 5-lipoxygenase inhibitor for the treatment of inflammatory diseases such as asthma, chronic obstructive pulmonary disease and atherosclerosis (Figure 1).[10]

As a result of the promising biological and pharmacological activities of neoflavones, several strategies have been developed for the construction of the 4-arylcoumarin framework. Classically, neoflavones have been synthesized using the Pechmann, Perkin, Ponndorf, Houben-Hösch and Knoevenagel reactions.[11] In recent years, transition metal catalyzed reactions have emerged as vital synthetic tools for the preparation of pharmacologically relevant heterocycles. Two synthetic strategies have been developed for the assembly of the neoflavone framework: the first one involves the formation of the pyrone ring by hydroarylation of alkynes,[12] or by reaction of the alkenyl C-H bond with carbon dioxide.[13] The second one relies on cross-coupling reactions of position 4 of activated coumarins with organometallic reagents.[14]

In recent years, site-selective cross coupling reactions of bis(halides) or bis(triflates) have been developed as a promising synthetic tool.[15] In this context, palladium catalyzed cross-coupling reactions of coumarin derivatives have also been reported.[16] Herein, we report what are, to the best of our knowledge, the first Suzuki-Miyaura coupling reaction of the bis(triflate) of 4,7-dihydroxycoumarin. The reactions, which proceed with excellent regioselectivity in favour of position 4, provide a convenient approach to various arylated coumarin derivatives which are not readily available by other methods.

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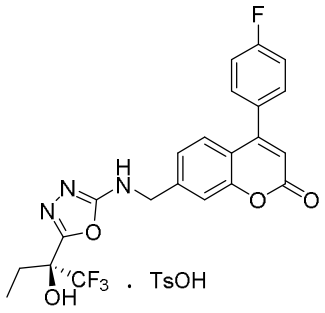
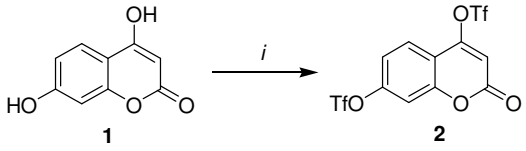
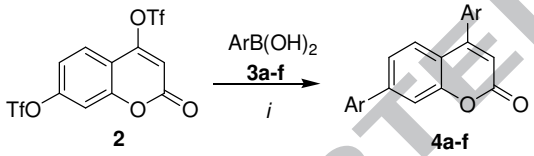


Figure 1. A 5-lipoxygenase inhibitor developed by Merck

The reaction of 4,7-dihydroxycoumarin (**1**) with triflic anhydride gave bis(triflate) **2** (Scheme 1).[17] The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a-f** (2.4 equiv) afforded 4,7-diarylcoumarins **4a-f** in 65-81% yield (Scheme 2, Table 1).[18,19] Both electron rich and poor arylboronic acids were successfully employed.



Scheme1. Synthesis of **2**, *Conditions; i*, **1** (1.0 equiv.), pyridine (4.0 equiv.), CH_2Cl_2, Tf_2O (2.4 equiv.), 50°C, 4 h.



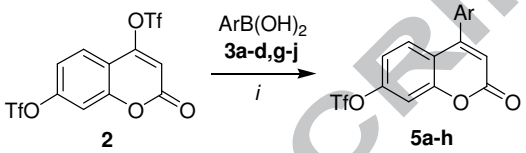
Scheme 2. Synthesis of **4a-f**, *Conditions*: *i*, **2** (1.0 equiv.), **3a-f** (2.4 equiv.), $Pd(PPh_3)_4$ (6 mol %), K_2CO_3 (2M), dioxane, 110 °C, 8 h.

Table 1. Synthesis of compounds **4a-f**

3,4	Ar	% (**4**)[a]
a	4-(MeO)C_6H_4	68
b	4-MeC_6H_4	79
c	4-(EtO)C_6H_4	66
d	3,5-$Me_2C_6H_3$	81
e	4-(F_3C)C_6H_4	65
f	C_6H_5	79

[a] Yield of isolated products

The Suzuki–Miyaura reaction of **2** with one equivalent of arylboronic acids afforded the 4-aryl-7-(trifluormethanesulfonyloxy)coumarins **5a-h** in 64-82 % yield (Scheme 3, Table 2).[20,21] The reactions proceeded by site-selectivity attack onto 4-position. During the optimization, it proved to be important to carry out the reaction at lower temperature (65 °C) as compared to the synthesis of the diarylated coumarins. In addition, the employment of toluene (instead of dioxane) proved to be important to optimize the yield. This might be explained by the solubility of the starting materials or change of the reactivity of the catalytic system by the solvent. Again, both electron rich and poor arylboronic acids gave good yields. The structure of **5d** was independently confirmed by X-ray crystal structure analyses (Figure 2).[22]



Scheme 3. Synthesis of **5a-h**, *Conditions: i*, **2** (1.0 equiv.), **3a-d,g-j** (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (2M), toluene, 65 °C, 6 h.

Table 2. Synthesis of compounds **5a-h**

3	5	Ar	% (**5**)[a]
a	**a**	4-(MeO)C_6H_4	71
b	**b**	4-MeC_6H_4	75
c	**c**	4-(EtO)C_6H_4	78
d	**d**	3,5-$Me_2C_6H_5$	82
g	**e**	4-EtC_6H_4	73
h	**f**	2-FC_6H_4	64
i	**g**	3,4,5-(MeO)$_3C_6H_2$	67
j	**h**	4-(F_3CO)C_6H_4	65

[a] Yield of isolated products

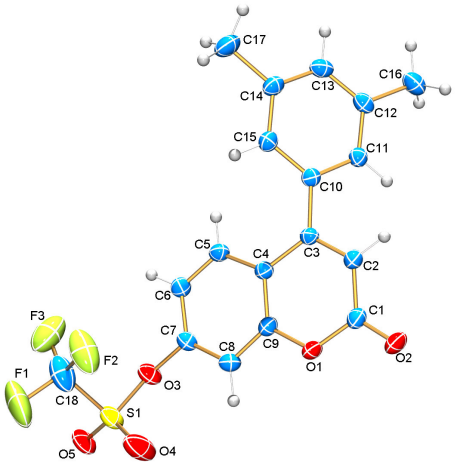


Figure 2. Ortep plot for compound **5d**

The one-pot reaction of **2** with two different arylboronic acids (sequential addition) afforded the diarylated coumarin **6** in

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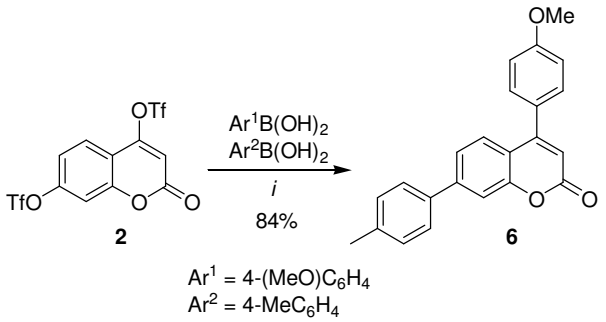
65% yield (Scheme 4, Table 3).[23,24] A fresh portion of the catalyst and of solvent (dioxane) had to be added to the reaction mixture in the second step in order to obtain a good yield of diarylated coumarin **6**.



Scheme 4. Synthesis of **6**. *Conditions: i*, 1) **2** (1.0 equiv.), (4-(MeO)C_6H_4)B$(OH)_2$ (1.0 equiv.), $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (2M), toluene, 65 °C, 6 h; 2) (4-MeC_6H_4)B$(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (6 mol %), K_2CO_3 (2M), dioxane, 110 °C, 6 h.

In conclusion, we have reported the first Suzuki–Miyaura reactions of 4,7-bis(trifluoromethylsulfonyloxy)coumarin. These reactions provide a convenient access to a variety of arylated coumarins. The reactions proceeded with very good site-selectivity in favour of 4-position. Palladium catalyzed cross-coupling reactions of polyhalogenated substrates or of bis(triflates) usually proceed in favour of the sterically less hindered and electronically more deficient position.[15] Position 4 is sterically more hindered than position 7, due to its location next to the annulated benzene ring. The selectivity can be explained by the highly electron deficient character of the 4-position of the coumarin moiety (electron-withdrawing effect of the carbonyl group).

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Z.; Patonay, T.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2013**, *54*, 3568.

17. **Synthesis of 2-oxo-2*H*-chromene-4,7-diyl bis(trifluoromethanesulfonate) (2).** To a CH_2Cl_2 solution (50 ml) of **1** (1.0 g, 5.6 mmole) was added pyridine (1.8 ml, 22.4 mmole) and the solution was stirred at 20°C for 10 min. under argon atmosphere. Then Tf_2O (2.3 ml, 13.44 mmole) was added at 20°C and the reaction mixture was heated at 50 °C for 20 min. The reaction mixture was cooled to room temperature and filtered, the filtrate was concentrated in vacuo. The product **2** was isolated by column chromatography (flash silica gel, heptane/EtOAc) as a colorless solid (2.10 g, 85%); Mp: 79 -77 °C. ^{1}H NMR (300 MHz. $CDCl_3$): δ = 6.51 (s, 1H, C=CH), 7.27-7.32 (m, 2H, ArH), 7.74 (d, 1H, *J* = 8.7 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 105.6, 110.1, 111.6 (CH), 112.9 (C), 118.3 (q, $J_{F,C}$ = 320.1 Hz, CF_3), 118.6 (q, $J_{F,C}$ = 320.0 Hz, CF_3), 123.6 (CH), 151.4, 152.0, 154.9 (C), 157.3 (C=O). ^{19}F NMR (282.4, MHz): δ = -72.5, -72.4. IR (KBr, cm^{-1}): v = 3171, 2988 (w), 1755 (s), 1698, 1643 (w), 1577 (m), 1550, 1499, 1475, 1433 (w). GC-MS (EI, 70 eV): m/z (%) = 442 ([M]$^+$, 88), 426 (100), 356 (15), 276 (33), 234 (23), 195 (16), HRMS (EI, 70 eV) calcd. for $C_{11}H_4O_8F_6S_2$ [M]$^+$: 441.93145; found: 441.93087.

18. **General Procedure A for the synthesis of 4a-f.** A solution of **2** (0.045 mmol), K_2CO_3 (2M, 2 ml), $Pd(PPh_3)_4$ (6 mol %) and arylboronic acid (2.4 equiv.) in 1,4-dioxane (3 ml) was stirred at 110 °C for 6 h under argon atmosphere. To the reaction mixture H_2O (20 ml) and CH_2Cl_2 (25 ml) were added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried over (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

19. **Synthesis of 4,7-diphenyl-2*H*-chromen-2-one (4f).** Starting with **2** (20 mg, 0.045 mmol), **3f** (13 mg, 0.11 mmole), $Pd(PPh_3)_4$ (3 mg, 6 mole%), K_2CO_3 (2M, 2ml) and 1,4-dioxane (3 ml), **4f** was isolated as a white solid (10 mg, 79%), mp: 131-133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.31 (s, 1H, C=CH), 7.34-7.37 (m, 1H, ArH), 7.39-7.44 (m, 5H, ArH), 7.47-7.49 (m, 4H, ArH), 7.56 - 7.58 (m, 3H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 113.8, 114.4 (CH), 116.8 (C), 121.9, 126.2, 126.3 (CH), 126.5 (C), 127.4, 127.6, 127.9, 128.1, 128,7 (CH), 134.3, 138.0, 144.1, 153.6 (C), 162.1(C=O). v = 3133, 2788, 2729 (w), 1856, 1799, 1775 1633 (s), 1599, 1528, 1517, 1502, 1444, 1432 (w).GC-MS (EI, 70 eV): m/z (%) = 298 ([M]$^+$, 89), 297 (17), 271 (100), 241(28), 240 (11), 239 (32). HRMS (EI, 70 eV) calcd. for $C_{21}H_{14}O_2$ [M]$^+$: 298.09803; found: 298.09883.

20. **General procedure B for the synthesis of (5a-h).** A solution of **2** (0.045 mmole), K_2CO_3 (2M, 2ml), $Pd(PPh_3)_4$ (3 mole%) and arylboronic acid (1.0 equiv.) in toluene (3 ml) was stirred at 65 °C. for 6 h. under argon atmosphere. To the reaction mixture H_2O (20 ml) and CH_2Cl_2 (25 ml) were added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried over (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

21. **4-(4-Methoxyphenyl)-2-oxo-2*H*-chromen-7-yl trifluoromethanesulfonate (5a).** Starting with **2** (20 mg, 0.045 mmole), **3a** (7 mg, 0.045 mmole), $Pd(PPh_3)_4$ (1.5 mg, 3 mole%), K_2CO_3 (2M, 2ml), and toluene (3 ml), **5a** was isolated as a white solid (13 mg, 71 %), mp: 86-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OCH_3), 6.33 (s, 1H, C=CH), 6.95 (d, 2H, *J* = 8.7 Hz, ArH), 7.10 (dd, 1H, *J* = 8.9, 2.3 Hz, ArH), 7.24 (d, 1H, *J* = 2.3 Hz, ArH), 7.33 (d, 2H, *J* = 8.7 Hz, ArH), 7,59 (d, 1H, *J*= 8.9 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 110.8, 114.6, 114.3, 117.3 (CH), 118.3 (q, $J_{F,C}$ = 320.0 Hz, CF_3), 119.3, 126.6 (C), 128.9, 129.9 (CH), 150.8, 154.8, 159.7 (C), 161.2 (C=O). ^{19}F NMR (282.4, MHz): δ = -72.5. IR (KBr, cm^{-1}): v = 3039, 2967, 2929 (w), 1756, 1699 (s), 1651, 1645, 1596 (s), 1577, 1538, 1519, 1503, 1474, 1453 (w). GC-MS (EI, 70 eV): m/z (%) = 400 ([M]$^+$, 67), 240 (15), 211 (100), 183 (23), 240 (11), 168 (19). HRMS (EI, 70 eV) calcd. for $C_{17}H_{11}O_6F_3S_1$ [M]$^+$: 400.02197; found: 400.02229.

22. CCDC-xxx contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

23. **General procedure C for the synthesis of 6.** A solution of **2** (0.045 mmole), K_2CO_3 (2M, 2mL), $Pd(PPh_3)_4$ (3 mole%) and arylboronic acid (1.0 equiv.) in toluene (3 ml) was stirred at 65 °C. for 6 h. under argon atmosphere. After cooling to 20 °C, $Ar^2B(OH)_2$ (1.2 equiv.), K_2CO_3 (2M, 2ml), $Pd(PPh_3)_4$ (6 mole %) and 1,4-dioxane (2 ml) were added and reaction mixture was heated at 110 °C for further 6 h. to the reaction mixture H_2O (20 ml) and CH_2Cl_2 (25 ml) were added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried over (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptane/EtOAc).

24. **4-(4-Methoxyphenyl)-7-(*p*-tolyl)-2H-chromen-2-one (6).** Starting with **2** (20 mg, 0.045 mmol), **3a** (7 mg, 0.045 mmole), $Pd(PPh_3)_4$ (1.5 mg, 3 mole%), K_2CO_3 (2M, 2ml) and toluene (3 ml), and **3b** (7 mg, 0.054 mmol), $Pd(PPh_3)_4$ (3 mg, 6 mole%), K_2CO_3 (2M, 2ml) and 1,4-dioxane (2 ml), **6** was isolated as a white solid (13 mg, 84%), mp: 133-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.28 (s, 1H, C=CH), 7.01 (d, 2H, *J* = 8.7 Hz, ArH), 7.28 -7.33 (m, 1H, ArH), 7.37-7.41 (m, 6H, ArH), 7.53 (d, 2H, *J* = 8.00 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.5 (OCH_3), 114.2 (C), 114.4, 115.5 (CH), 118.0 (C), 122.9, 124.4 (CH), 127.6 (C), 127.9, 129.0, 129.3, 129.9 (CH), 138.8, 145.2, 152.5, 154.7, 155.2 (C), 161.2 (C=O). IR (KBr, cm^{-1}): v = 3012, 2878, 2822 (w), 1966, 1844 (s), 1744, 1696 (m), 1601, 1578, 1522, 1504 (w), 1487, 1454, 1412 (m).).GC-MS (EI, 70 eV): m/z (%) = 342 ([M]$^+$, 100), 318 (23), 280 (16), 234 (10), 187 (19). HRMS (EI, 70 eV) calcd. for $C_{23}H_{18}O_3$ [M]$^+$: 342.12505; found: 342.12459.