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Regioselective Suzuki–Miyaura cross-coupling reactions of 4-methyl-6,7-bis(trifluoromethanesulfonyloxy)coumarin

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ABSTRACT

Arylated coumarins were prepared by site-selective Suzuki–Miyaura cross-coupling reaction of the bis(triflate) of 4-methyl-6,7-dihydroxycoumarin.

Coumarin and its derivatives are one of the most important classes of heterocyclic compounds which occur in many natural products.[1] For example, wedelolactone and other coumarins were isolated from the roots of *Hedysarum multijugum*, which is a plant in *Hedysarum Linn.* of the family *Leguminosae* used as a folk herbal drug in northwest China.[1a] Many compounds were isolated from plants, such as alternariol, umbelliferone (7-hydroxycoumarin), scoparone (6,7-dimethoxycoumarin), osthole (7-methoxy-8-(3-methylbut-2-en-1-yl)coumarin), and others.[2] Coumarins are known to possess a wide range of biological activities, such as anti-HIV, antibiotic, antifungal, anti-bacterial (including antituberculotic), antiviral, anticancer, immunosuppressive, muscle relaxant, anticlotting, and anticoagulant activity.[3] In addition, they are widely used as additives in food chemicals, perfumes, agrochemicals, cosmetics, pharmaceuticals,[4] insecticides, optical brightening agents, and dispersed fluorescent and laser dyes.[5] Coumarins can be synthesized by various methods, such as the Pechmann,[6] Perkin,[7] Knoevenagel,[8] and Wittig[9] reaction. Because of its preparative simplicity and relatively inexpensive starting materials, the Pechmann reaction has been widely used for the synthesis of coumarins. This method involves the reaction of phenols with β-ketoesters in the presence of acidic catalysts.[10–12] Transition-metal catalyzed reactions have also been applied to the synthesis of coumarins substituted at positions three or four. Cross-coupling reactions of 4-tosyloxycoumarins have been widely investigated. Palladium,[13] nickel,[14] and rhodium catalysts[15] have been used in Suzuki–Miyaura reactions of arylboronic acids. Suzuki–Miyaura reactions using potassium aryltrifluoroborates have also been reported.[16] Likewise, the applicability of Negishi,[17] Sonogashira,[17] Stille,[18] and Heck[19] reactions in the coumarin series has been demonstrated. On the other hand, not much is known about palladium catalyzed cross-coupling reactions of more complex coumarins. A study related to reactions of 3-bromo-4-(trifluoromethanesulfonyloxy)- and 3-bromo-4-tosyloxy-coumarin has been previously reported.[20] Cross-coupling reactions of 5,7-bis(trifluoromethanesulfonyloxy)-coumarin and of 3- and 6-bromo-4-(trifluoromethane-sulfonyloxy) coumarin have also been reported.[21]

Herein, we report a new and convenient synthesis of arylated coumarins by what are, to the best of our knowledge, the first Suzuki–Miyaura cross-coupling reactions of the bis(triflate) of 4-methyl-6,7-dihydroxycoumarin. The reactions proceed with very good regioselectivity and the products are not readily available by other methods.

4-Methyl-6,7-dihdroxycoumarin (**1**) was transformed to its bis(triflate) **2** in 75% yield by reaction with triflic anhydride (2.4 equiv) and triethylamine (4.0 equiv) (Scheme 1).[22] It proved

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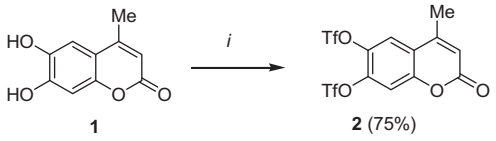
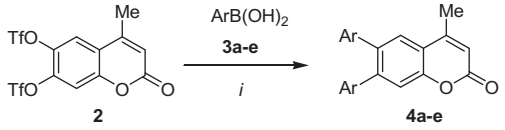


Scheme 1. Synthesis of **2**. Reagents and conditions: (i) **1** (1.0 equiv), Et_3N (4.0 equiv), (CH_2Cl_2, 20 °C; **2**) Tf_2O (2.4 equiv), −78 to 20 °C, 6 h.



Scheme 2. Synthesis of **4a–e**. Reagents and conditions: (i) **2** (1.0 equiv), **3** (2.0 equiv), K_3PO_4 (3.0 equiv), $Pd(PPh_3)_4$ (6 mol %), 1,4-dioxane, 120 °C, 6 h.

Table 1
Synthesis of **4a–e**

3, 4	Ar	4[a] (%)
a	3,5-$Me_2C_6H_3$	75
b	4-(MeO)C_6H_4	83
c	4-ClC_6H_4	83
d	C_6H_5	70
e	4-(EtO)C_6H_4	88

[a] Yields of isolated products.

to be important that the addition of triflic anhydride was performed at −78 °C.

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a–e** (2.0 equiv) afforded the 4-methyl-6,7-diarylcoumarins **4a–e** in 73–88% yield (Scheme 2, Table 1).[23,24] Both electron-poor and electron-rich arylboronic acids were successfully employed. The best yields were obtained using $Pd(PPh_3)_4$ (6 mol %) as the catalyst, K_3PO_4 (3.0 equiv) as the base, and 1,4-dioxane as the solvent (120 °C, 6 h). The structure of **4e** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[25]

The Suzuki–Miyaura reaction of **2** with 1.2 equiv of arylboronic acids **3** afforded the 4-methyl-7-aryl-6-(trifluoromethanesulfonyloxy)coumarins **5a–m** in 70–90% yield with very good regioselectivity (Scheme 3, Table 2).[23,26] During the optimization, it proved to be important to use 1.2 equiv of the arylboronic acid and to carry out the reaction at 70 instead of 120 °C to avoid double coupling. Both electron-poor and electron-rich arylboronic acids were successfully employed. The structure of **5b** was confirmed by HMBC experiments (Fig. 2). The structure of **5f** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[25]

The one-pot Suzuki–Miyaura reaction of bis(triflate) **2** with two different arylboronic acids (sequential addition of 1.2 equiv of each arylboronic acid) afforded the 4-methyl-6,7-diarylcoumarins **6a–d** in 73–81% yields (Scheme 4, Table 3).[23,27] The reactions were carried out at 70 °C for the first step (to avoid double coupling) and at 120 °C for the second step.

Palladium catalyzed cross-coupling reactions usually occur at the electronically more deficient and sterically less hindered position.[28,29] Positions six and seven of bis(triflate) **2** are sterically similar. However, the regioselectivity of Suzuki reactions of bis(triflate) **2** in favor of position seven can be explained by electronic reasons. Position seven is located *para* to the electron-withdrawing vinylogous ester group, while position six is located *para* to the electron-donating oxygen atom.

In conclusion, we have reported a convenient synthesis of arylated coumarins by Suzuki–Miyaura cross-coupling reactions of

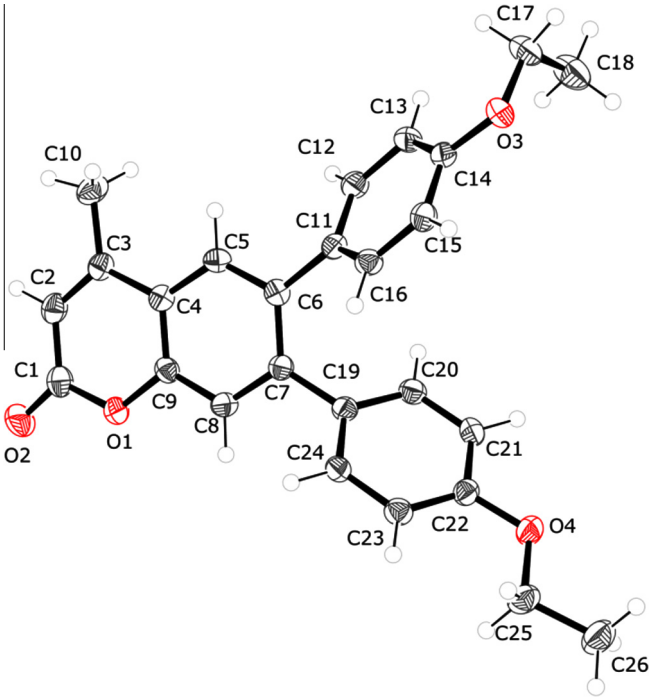
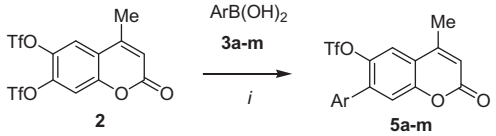


Figure 1. Molecular structure of **4e**.



Scheme 3. Synthesis of **5a–m**. Reagents and conditions: (i) **2** (1.0 equiv), **3** (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 70 °C, 6 h.

Table 2
Synthesis of **5a–m**

3, 5	Ar	5[a] (%)
a	3,5-$Me_2C_6H_3$	75
b	4-(MeO)C_6H_4	80
c	4-ClC_6H_4	85
d	C_6H_5	72
e	4-(EtO)C_6H_6	90
f	4-EtC_6H_4	84
g	4-FC_6H_4	78
h	4-(F_3C)C_6H_4	83
i	4-MeC_6H_4	75
j	3-MeC_6H_4	80
k	3-(MeO)C_6H_4	70
l	2,3,4-$(MeO)_3C_6H_2$	90
m	4-*t*BuC_6H_4	77

[a] Yields of isolated products.

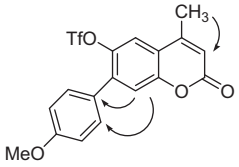


Figure 2. Important HMBC correlations of **5b**.

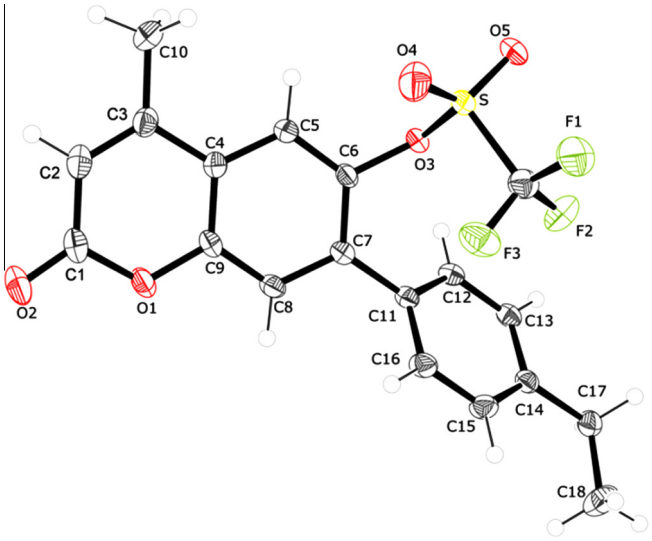
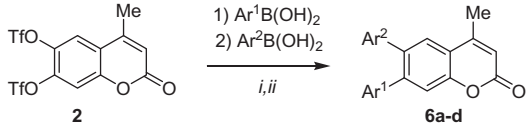


Figure 3. Molecular structure of **5f**.



Scheme 4. Synthesis of **6a–d**. Reagents and conditions: (i) **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), dioxane, 70 °C, 6 h; (ii) $Ar^2B(OH)_2$ (1.2 equiv), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (3 mol %), 1,4-dioxane, 120 °C, 6 h.

Table 3
Synthesis of **6a–d**

3	6	Ar^1	Ar^2	6[a] (%)
b,**c**	**a**	4-(MeO)C_6H_4	4-ClC_6H_4	73
b,**g**	**b**	4-(MeO)C_6H_4	4-FC_6H_4	78
b,**j**	**c**	4-(MeO)C_6H_4	3-MeC_6H_4	75
b,**a**	**d**	4-(MeO)C_6H_4	3,5-$Me_2C_6H_3$	81

[a] Yields of isolated products.

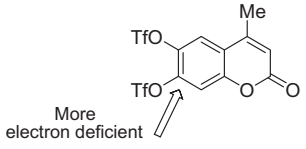


Figure 4. Possible explanation for the site-selectivity of **2**.

the bis(triflate) of 4-methyl-6,7-dihydroxycoumarin. The reactions proceed with excellent regioselectivity in favor of the electronically more deficient position (Fig. 4).

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22. *4-Methyl-2-oxo-2H-chromene-6,7-diyl bis(trifluoromethane-sulfonate) (**2**):* To a solution of 4-methyl-6,7-dihydroxycoumarin (**1**) (0.5 g, 2.60 mmol) in CH_2Cl_2 (30 mL) was added triethylamine (0.36 mL, 10.4 mmol) at room temperature under an argon atmosphere. After 10 min, Tf_2O (1.0 mL, 6.2 mmol) was added at −78 °C. The mixture was allowed to warm to 20 °C and stirred for 6 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptane/EtOAc = 8:2) without aqueous work up to give (**1**) as a white solid (0.9 g, 75%); mp 125–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (d, J = 1.5 Hz, CH_3), 6.37 (d, J = 1.2 Hz, 1H), 7.41 (br s , 1H, ArH), 7.59 (br s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 18.6 (CH_3), 110.9, 112.7, 113.1 (CH), 116.0 (q, $J_{F,C}$ = 317.0 Hz, CF_3), 117.3 (q, $J_{F,C}$ = 317.0 Hz, CF_3), 118.1, 136.4, 141.7, 150.5, 152.6 (C), 158.2 (CO). ^{19}F NMR (282.4, MHz): δ = −72.8, −72.7. IR (KBr, cm^{-1}): ν = 3124, 3053, 2964, 2926 (w), 1740 (s), 1673, 1625, 1613, 1570 (w), 1498 (m). GC–MS (EI, 70 eV): m/z (%) = 456 ($[M]^+$, 100), 324 (10), 323 (84), 232 (10), 203

(33), 162 (13), 134 (26), 69 (55). HRMS (EI, 70 eV) calcd for $C_{12}H_6F_6O_8S_2$ ([M]$^+$): 455.94028, found: 455.94130.

23. *General procedure for Suzuki–Miyaura reactions:* A solution of K_3PO_4, $Pd(PPh_3)_4$, and arylboronic acid in the solvent indicated was stirred at the indicated temperature and for the indicated time. After cooling to 20 °C, distilled H_2O was added. The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (flash silica gel, heptanes–EtOAc).
24. *6,7-Bis(3,5-dimethlyphenyl)-4-methyl-2H-chromen-2-one (**4a**):* Starting with **2** (70 mg, 0.153 mmol), 3,5-dimethlyphenylboronic acid (**3a**) (51 mg, 0.337 mmol), $Pd(PPh_3)_4$ (11 mg, 6 mol %, 0.009 mmol), K_3PO_4 (98 mg, 0.460 mmol), and 1,4-dioxane (3 mL), **4a** was isolated as a white solid (42 mg, 75%); mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 6H, CH_3), 2.14 (s, 6H, CH_3), 2.39 (d, J = 1.3 Hz, 3H, CH_3), 6.24 (d, J = 1.2 Hz, 1H), 6.67–6.80 (m, 6H, ArH), 7.30 (br s, 1H, ArH) , 7.49 (br s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 ($2CH_3$), 20.1 ($2CH_3$), 26.1 (CH_3), 113.9, 117.2 (CH), 117.7, 120.1 (C), 125.1, 126.4, 126.6, 127.4, 127.9 (CH), 136.3, 136.3, 138.5, 139.1, 143.7, 151.2, 151.5, 154.4, 156.1 (C), 160.9 (CO). IR (KBr, cm^{-1}): ν = 3015, 3082, 3066, 2868, 2732, 2645 (w), 1722 (s), 1618, 1607 (m), 1573, 1537, 1516, 1485 (w). GC–MS (EI, 70 eV): m/z (%) = 368 ([M]$^+$,100), 353 (12), 338 (10). HRMS (EI, 70 eV) calcd for $C_{26}H_{24}O_2$ [M]$^+$: 368.17708; found: 368.17685.
25. CCDC-934927 and 934928 contain all crystallographic details of this publication and is available free of charge at http://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.
26. *7-[(3,5-Dimethylphenyl)-4-methyl-2-oxo-2H-chromen-6-yl] trifluoromethanesulfonate (**5a**):* Starting with **2** (70 mg, 0.153 mmol), 3,5-dimethlyphenylboronic acid (**3a**) (28 mg, 0.184 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol %, 0.005 mmol), K_3PO_4 (49 mg, 0.230 mmol), and dioxane (3 mL), **5a** was isolated as a white solid (47 mg, 75%); mp 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 6H, $2CH_3$), 2.31 (d, J = 1.4 Hz, 3H, CH_3), 6.31 (d, J = 1.4 Hz, 1H), 6.67 (br s, 1H, ArH), 7.17 (d, J = 8.8 Hz, 3H, ArH), 7.33 (d, J = 8.4 Hz, 1H, ArH), 7.48 (br s, 1H, ArH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 17.6 ($2CH_3$), 20.1 (CH_3), 113.9, 115.2, 118.7 (CH), 125.4 (q, $J_{F,C}$ = 320.4 Hz, CF_3), 126.4, 127.9 (CH), 129.8, 132.8, 136.3, 137.3, 138.4, 141.5, 149.8, 151.3 (C), 160.1 (CO). ^{19}F NMR (282.4 MHz): δ = −73.8. IR (KBr, cm^{-1}): ν = 3057, 2950, 2910, 2838 (w), 1721 (s), 1611, 1606 (m),1538 (w), 1509, 1491 (m). GC–MS (EI, 70 eV): m/z (%) = 412 ([M]$^+$, 100), 280 (20), 279 (30), 264 (12), 235 (11). HRMS (EI, 70 eV) calcd for $C_{19}H_{15}F_3O_5S$ [M]$^+$: 412.05868; found: 412.05840.
27. *6-(4-Chlorophenyl)-7-(4-methoxyphenyl)-4-methyl-2H-chromen-2-one (**6a**):* The reaction was carried out in a one-pot procedure with sequential addition of the boronic acids to the substrate **2**. Catalyst and base had to be added two times. Starting with **2** (70 mg, 0.153 mmol), 4-methoxyphenylboronic acid (**3b**) (28 mg, 0.153 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol %, 0.005 mmol), K_3PO_4 (49 mg, 0.2301 mmol), 4-chlorophenylboronic acid (**3c**) (28 mg, 0.153 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol %, 0.005 mmol), K_3PO_4 (49 mg, 0.230 mmol), and dioxane (3 mL), **6a** was isolated as a white solid (42 mg, 73%); mp 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (d, J = 1.1 Hz, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.24 (d, J = 1.3 Hz, 1H), 6.72 (d, J = 8.1 Hz, 2H, ArH), 6.95–6.99 (m, 5H, ArH), 7.16 (d, J = 8.1 Hz, 2H, ArH), 7.46 (br s, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.6 (CH_3), 54.2 (OCH_3), 112.7, 114.1, 117.4 (CH), 117.8 (C), 125.3, 127.4, 129.8, 130.0 (CH), 130.5, 132.0, 134.7, 137.8, 143.1, 151.0, 151.9, 158.1 (C), 159.7 (CO). IR (KBr, cm^{-1}): ν = 3115, 3092, 3076, 2966, 2932, 2845 (w), 1731 (s), 1620, 1600 (m), 1580, 1540, 1522, 1493 (w). GC–MS (EI, 70 eV): m/z (%) = 376 ([M]$^+$, [^{35}Cl], 100), 348 (13). HRMS (EI, 70 eV) calcd for $C_{23}H_{17}{}^{35}ClO_3$ ([M]$^+$): 376.08607; found 367.08589.
28. For reviews of cross-coupling reactions of polyhalogenated heterocycles and triflates, see: (a) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245; (b) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283; (c) Rossi, R.; Bellina, F.; Lessi, M. *Adv. Synth. Catal.* **2012**, *354*, 1181.
29. For a simple guide to predict the regioselectivity of Pd catalyzed cross-coupling reactions, see: Handy, S. T.; Zhang, Y. *Chem. Commun.* **2006**, 299.