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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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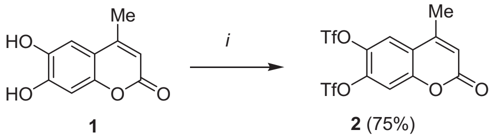
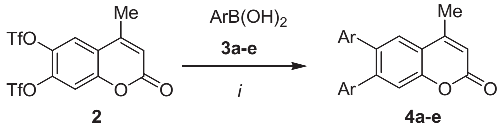


Scheme 1. Synthesis of **2**. Reagents and conditions: (i) **1** (1.0 equiv), Et_3N (4.0 equiv), (CH_2Cl_2, 20 °C; **2**) Tf_2O (2.4 equiv), −78 to 20 °C, 6 h.



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

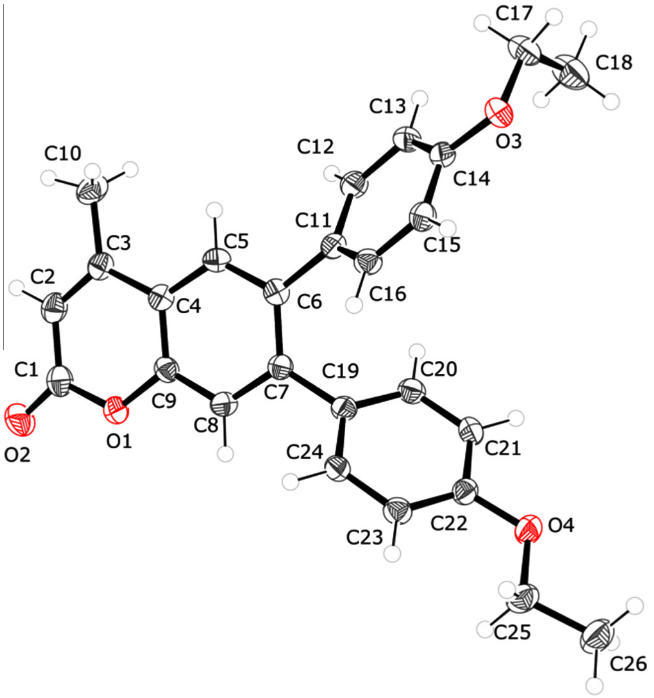
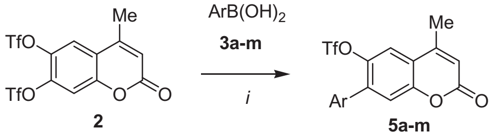


Figure 1. Molecular structure of **4e**.



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.

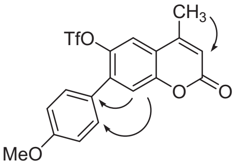


Figure 2. Important HMBC correlations of **5b**.