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Synthesis of *gem*-difluoromethylenated biflavonoid via the Suzuki coupling reaction

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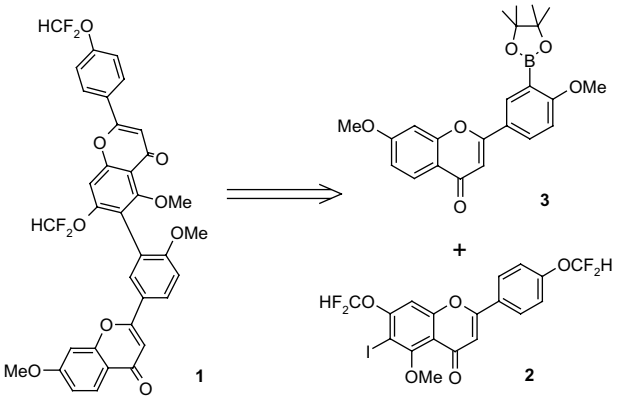
Abstract—*gem*-Difluoromethylenated biflavonoid **1** was synthesized via the Suzuki coupling reaction. The key intermediate 6-iodonated flavone **4** was regioselectively synthesized by the use of $AgOAc/I_2$ under mild conditions without handling of a strongly toxic reagent. The key step was the formation of a flavone 3′-boronate **3** using a palladium-catalyzed exchange of the corresponding 3′-iodonated flavone with a diboron reagent.

Biflavonoids are a group of naturally occurring compounds and possess a broad range of pharmacological properties including anti-oxidant, anti-microbial, anti-inflammatory and anti-cancer properties.[1–3] However, the anti-cancer activity of biflavonoids is low. It is known that fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen. The introduction of the trifluoromethyl (CF_3) or *gem*-difluoromethylene (CF_2) group into organic molecules often changes their physiological, physical and chemical properties dramatically, without extra steric demand. We have recently reported that introduction of CF_3 group into flavonoids molecule can enhance their anti-cancer activities.[4,5] Despite the wide occurrence and biological importance of biflavonoids, synthetic efforts towards efficient preparation of fluorinated biflavonoids are rarely reported. As a part of our current work on the search for anti-cancer substances with high efficacy, low toxicity and minimum of side effects, we describe herein the synthesis of *gem*-difluoromethylenated biflavonoid **1**.

We envisaged that **1** could be constructed from 6-iodoflavone **2** and the 3′-boronate **3** via a Suzuki coupling reaction (Scheme 1).



Scheme 1. Retrosynthetic analysis.

Compound **2** was prepared as outlined in Scheme 2. Condensation of phloroglucinol with chloroacetonitrile catalyzed by $ZnCl_2$ and HCl gas followed by hydrolysis provided ketone **7** in 65% yield. Treatment of **7** with *p*-hydroxytolualdehyde in the presence of excess NaOH in H_2O/EtOH and followed by acidification with aqueous HCl gave the expected compound **6** in 92% yield.[6] Based on our knowledge of the chemistry of flavonoids, the 5-hydroxy group of **6** was hydrogen bonded to the adjacent carbonyl group, and thus not readily *gem*-difluoromethylenated.[7] Chemoselective 4′-*O*- and 7-*O*-*gem*-difluoromethylenation of **6** was therefore readily achieved using HCF_2Cl gas in the presence of NaOH

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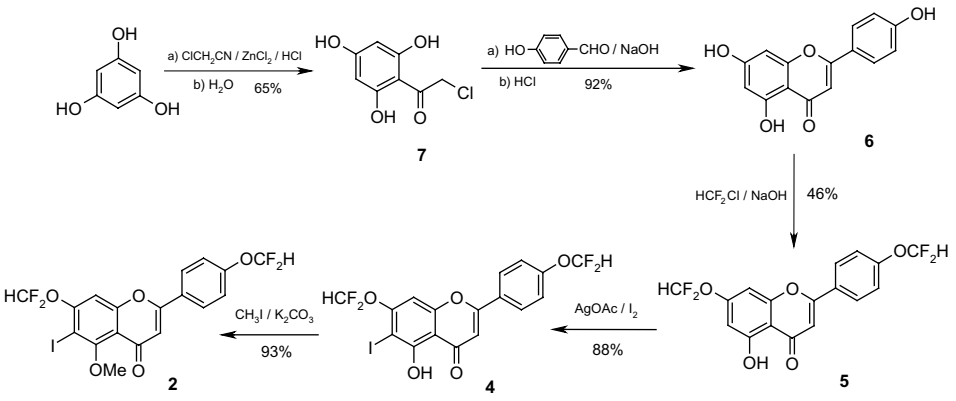
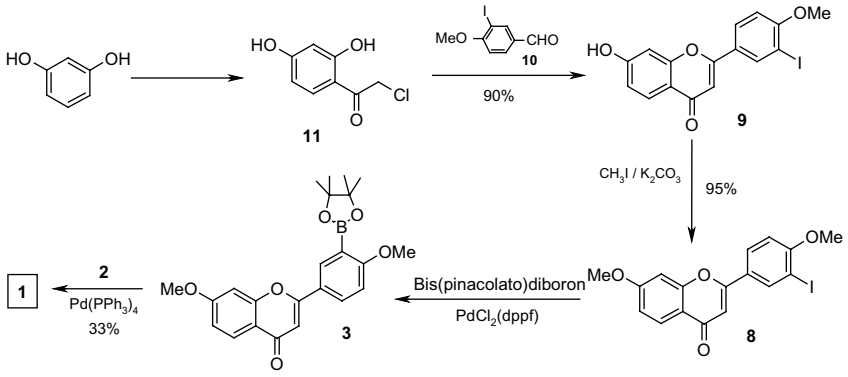


Scheme 2.



Scheme 3.

in dioxane/H_2O and compound **5** was obtained in 46% yield.[8] The iodination of 5,7-dioxygenated flavones are known to occur rather at C8.[4,9] To our best knowledge, there were two methodologies, to provide 6-iodoflavones in good yield in the literature. One of them required TlOAc, a highly toxic reagent,[10] the other was regioselective 6-iodination of 5,7-dioxygenated flavones by the use of benzyltrimethylammonium dichloroiodate.[9] We regioselectively prepared 6-iodonated flavone **4** in 88% yield from compound **5** with AgOAc/I_2 under mild conditions.[11] The methylation of **4** was accomplished with CH_3I in the presence of K_2CO_3 to give compound **2** in 93% yield.

Compound **3** was prepared according to Scheme 3. Compound **11** was prepared from resorcinol in the same manner as compound **7**. Compound **10,** prepared from 4-methoxybenzaldehyde with ICl in AcOH at 60 °C, was reacted with **11** in the presence of excess NaOH in H_2O/EtOH and followed by acidification with aqueous HCl to give the expected compound **9** in 90% yield. The methylation of **9** was carried out with CH_3I in the presence of K_2CO_3 in acetone to afford **8** in 95% yield. Following the literature procedure,[10] a mixture of compound **8**, bis(pinacolato)diboron, KOAc and $PdCl_2$(dppf) in DMF was stirred at 80 °C overnight. The expected compound **3** was obtained by column chromatography on silica gel. The cross coupling of compound **3** with **2** by a standard Suzuki reaction conditions[12] gave the desired biflavonoid **1**[13] in 33% yield based on compound **8**.

In summary, we have described a synthesis of *gem*-difluoromethylenated biflavonoid **1** via the Suzuki coupling reaction. The key intermediate 6-iodonated flavone **4** was regioselectively synthesized by the use of AgOAc/I_2 under mild conditions without the handling of a strongly toxic reagent.

Acknowledgements

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11. The experimental procedure for the conversion of **5** to **4**: To a solution of **5** (310 mg, 0.8 mmol) in CH_2Cl_2 (30 mL) was added silver acetate (158 mg, 0.9 mmol). Then a solution of iodine (230 mg, 0.9 mmol) in CH_2Cl_2 (40 mL) was added dropwise over 1 h. After stirring the resulting mixture at room temperature for 36 h, the reaction mixture was filtered and the precipitated silver iodide was washed with CH_2Cl_2. The combined filtrates were washed with a 10% aqueous solution of Na_2SO_3, brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel (petroleum ether–CH_2Cl_2 = 1:1) to give **4**.
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13. Physical data for some new compounds. Compound **1** mp 177–179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.87 (3H, s), 3.97 (3H, s), 4.00 (3H, s), 6.86 (1H, s), 6.92 (1H, dd, J = 2.0, 8.8 Hz), 7.06 (1H, s), 7.17 (1H, d, J = 8.8 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.39 (1H, t, J = 72.4 Hz), 7.43 (2H, d, J = 8.8 Hz), 7.48 (1H, t, J = 73.2 Hz), 7.61 (1H, s), 7.74 (1H, d, J = 8.8 Hz), 8.05 (1H, dd, J = 2.0, 8.8 Hz), 8.24 (2H, d, J = 8.8 Hz), 8.46 (1H, d, J = 2.0 Hz); ^{19}F NMR (376 MHz): δ −83.09 (d, J = 73.2 Hz), −83.78 (d, J = 72.4 Hz). Anal. Calcd for $C_{35}H_{24}F_4O_9$: C, 63.26; H, 3.64. Found: C, 63.11; H, 4.08. Compound **2** mp 230–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (3H, s), 6.00 (1H, t, J = 72.8 Hz), 6.68 (1H, t, J = 72.0 Hz), 6.69 (1H, s), 7.17 (2H, d, J = 8.8 Hz), 7.18 (1H, s), 7.88 (2H, d, J = 8.8 Hz). ^{19}F NMR (376 MHz): δ −82.36 (d, J = 72.8 Hz), −81.70 (d, J = 72.0 Hz); HRMS Calcd for $C_{18}H_{11}IF_4O_5$: 509.9587; Found: 509.9545. Compound **4** mp 236–238 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.64 (1H, t, J = 73.2 Hz), 6.69 (1H, t, J = 72.3 Hz), 6.77 (1H, s), 6.93 (1H, s), 7.30 (2H, d, J = 9.0 Hz), 7.94 (2H, d, J = 9.0 Hz), 13.82 (1H, s). ^{19}F NMR (282 MHz): δ −82.33 (d, J = 73.2 Hz), −81.99 (d, J = 72.3 Hz); HRMS Calcd for $C_{17}H_9IO_5F_4$: 495.9411; Found: 495.9411. Compound **5** mp 151–152 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (1H, d, J = 2.1 Hz), 6.63 (1H, t, J = 72.6 Hz), 6.64 (1H, t, J = 72.9 Hz), 6.69 (1H, s), 6.75 (1H, d, J = 2.1 Hz), 7.29 (2H, d, J = 8.1 Hz), 7.92 (2H, d, J = 8.1 Hz). ^{19}F NMR (282 MHz): δ −82.59 (d, J = 72.9 Hz), −82.08 (d, J = 72.6 Hz); Anal. Calcd for $C_{17}H_{10}F_4O_5$: C, 55.15; H, 2.72. Found: C, 55.12; H, 2.80.