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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3707–3709

Efficient synthesis of isoflavone analogues via a Suzuki coupling reaction

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Received 5 March 2005; revised 16 March 2005; accepted 21 March 2005
Available online 8 April 2005

Abstract—Analogues of 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-one were synthesized with high yields via the Suzuki coupling reaction of 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one with different aryl boronic acids.
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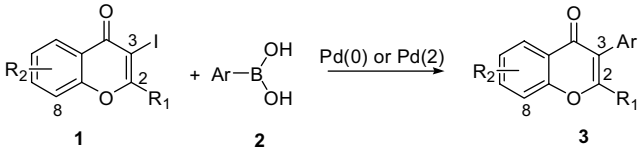
Isoflavones (3-aryl-chromen-4-ones) (**3**) represent a large class of natural products and exhibit remarkably diverse biological properties. They are found in many plants and are especially abundant in legumes (Fabaceae), such as soya, lentils, chick pea, fenugreek, clovers, and alfalfa. Compounds with isoflavone as the core structure have been shown to possess antioxidant,[1,2] antitumor,[3,4] anticataracts,[5] antiinflammatory,[6] and antifertility[7] activity. Some isoflavones are well-known tyrosine kinase inhibitors[8] and studies also show that isoflavones bind to G-protein coupled receptors, including serotonin, dopamine, δ-opiate, and benzodiazepine receptors.[9]

With their remarkably rich biological activities and excellent pharmacological properties, isoflavone-based compounds have been the target of a great deal of research into their synthesis. Almost all of the published synthetic methods used the cyclization of 2-hydroxyaryl alkyl ketones under acidic or basic conditions as the key step.[10–12] Although these methods can produce isoflavones individually in good yield, they are not efficient for synthesis of a series of isoflavones with different substituted groups at the 3-position. Here, we described a synthetic method that can be used to obtain a series of 3-aryl isoflavones efficiently via a Suzuki reaction by using 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one as the general intermediate.

Our synthetic route is shown in Scheme 1. Efficient synthetic methods have been reported to obtain 3-halide-chromen-4-ones **1**[13] and coupling of **1** with different boronic acids **2** via Suzuki reaction may afford 3-aryl-isoflavones **3**.

First, 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one was prepared in six steps (Scheme 2). Using 3,4,5-trimethoxy-phenol **4** as the starting material, **5** was obtained by a Friedel–Crafts reaction. With aluminum chloride as the catalyst, the yield was quite low (10–20%), and there were other unidentified byproducts, possibly caused by the removal of the methoxyl groups in **4** by aluminum chloride. We therefore used a somewhat weaker Lewis acid–boron trifluoride diethyl etherate as the catalyst, which gave a satisfactory yield (80%). The next step was reduction of the carbonyl group in compound **5** to a methylene group. Surprisingly we found that it was difficult to obtain **6** by hydrogenation of **5**, which might be attributed to the formation of an intramolecular hydrogen bond between the carbonyl group and the hydroxyl group in **5**. Instead, compound **6** was generated in an excellent yield



1 2 3

Scheme 1. General synthetic route of 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-ones.

Keywords: Isoflavone; Synthesis; Suzuki coupling reaction.
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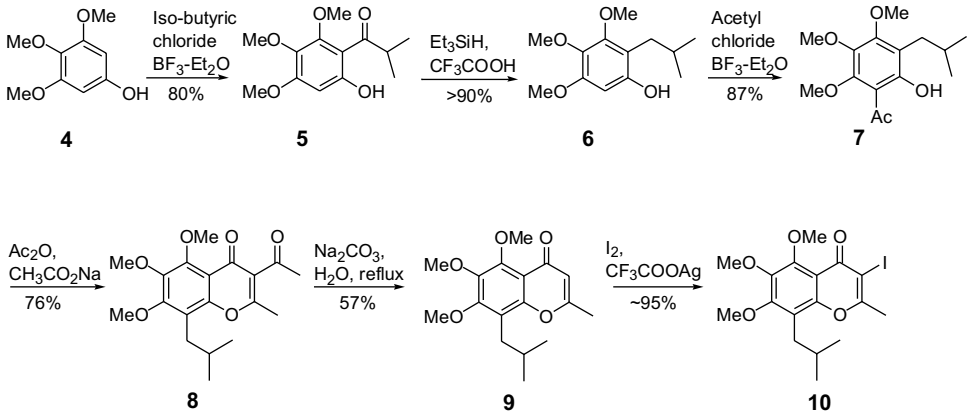
doi:10.1016/j.tetlet.2005.03.143



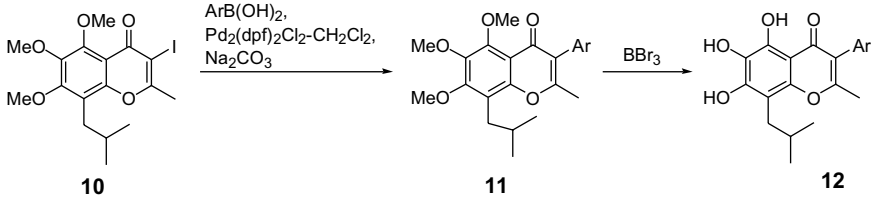
Scheme 2. Synthesis of 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one.

(>90%) by treating **5** with triethylsilane in trifluoroacetic acid, followed by another Friedel–Crafts reaction to generate compound **7** in 87% yield. Using a known procedure,[14] compound **8** was obtained. The acetyl group in 3-position in **8** could be removed easily in basic condition to generate **9** in a yield of 57%. The moderate yield of deacylation was due to the generation of a by-product. Compound **9** was treated with I_2 in the presence of CF_3CO_2Ag as the catalyst to obtain compound **10** in almost quantitative yield.

With 3-iodo-8-isobutyl-5,6,7-trimethoxy-2-methyl-4*H*-chromen-4-one **10** in hand, we explored the Suzuki coupling reaction of **10** with different boronic acids. Treatment of compound **11** with benzeneboronic acid using $Pd(Ph_3P)_4$ as the catalyst gave **11a** in a 60% yield. When [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)–CH_2Cl_2 ($Pd(dpf)_2Cl_2$–CH_2Cl_2) was used as the catalyst, the yield was improved to 85% and this catalyst was therefore used for further exploration (Table 1). We treated compound **10** with different aromatic boronic acids and obtained 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-one in excellent yield in most cases (Table 1). The low yield of **11**: might be due to some impurity in 4-benzenesulfonyl-phenyl boronic acid, which was prepared in our laboratory. Finally, treatment of **12** with BBr_3 at −78 °C and slowly raising the reaction to room temperature generated analogues of 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-one (**12**) in satisfied yield.[15]

In summary, an efficient method was developed to synthesize a library of isoflavones 3-aryl-4*H*-chromen-4-ones with different substituents at the 3-position.

Table 1. Synthesis of 3-aryl-8-isobutyl-5,6,7-trihydroxy-2-methyl-4*H*-chromen-4-ones via Suzuki reaction



Entry	$ArB(OH)_2$	Compound **11**[a] (%)	Compound **12**[b] (%)
a	Ar = phenyl	85	73
b	2-Naphthyl	87	73
c	4-Cl-phenyl	85	76
d	4-MeO-phenyl	89	68[c]
e	4-PhO-phenyl	79	80
f	4-CO_2H-phenyl	75	65[d]
h	4-Phenyl-phenyl	87	71
i	4-Benzenesulfonyl-phenyl	50	75
j	6-EtO-2-naphthyl	75	65[e]
k	2-Thianaphenyl	43	75

[a] Reported yields are for pure isolated products after chromatography.
[b] Yields after chromatography and recrystallization.
[c] Yield for 5,6,7-trihydroxy-3-(4-hydroxy-phenyl)-2-methyl-chromen-4-one.
[d] Compound **11f** was reacted with aniline to get the amide and then *N*-phenyl-4-(5,6,7-trihydroxy-2-methyl-4-oxo-4*H*-chromen-3-yl)-benzamide was obtained by deprotection.
[e] 5,6,7-Trihydroxy-3-(6-hydroxy-naphthalen-2-yl)-8-isobutyl-2-methyl-chromen-4-one was obtained.

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15. Data for **12b**: ^{1}HNMR (300 MHz, $CDCl_3$): δ 13.11 (s, 1H); 8.16–7.86 (m, 3H); 7.80 (s, 1H); 7.56–7.52 (m, 2H); 7.42 (d, J = 8.40 Hz, 1H); 6.19 (s, 1H); 5.58 (s, 1H); 2.73 (d, J = 7.08 Hz, 2H); 2.38 (s, 3H); 2.04 (heptet, J = 5.9 Hz, 1H); 0.99 (d, J = 6.6 Hz, 6H). ^{13}CNMR (75 MHz, $CDCl_3$): δ 181.69; 164.31; 148.95; 148.90; 143.82; 133.32; 132.89; 129.63; 128.14; 128.08; 128.00; 127.72; 126.88; 126.33; 126.17; 120.95; 106.36; 104.34; 31.39; 28.65; 22.56; 19.57.