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[A0030]

APPLICATION OF SUZUKI COUPLING REACTION FOR PREPARATION OF SOME ARYLCHRYSIN ANALOGUES

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ABSTRACT

A new class of flavone which possess an aryl radical substituted in the A ring via C-C bond, arylchrysin analogues, has been synthesized from chrysin by Suzuki coupling reaction in three to five steps. Firstly, methylation or benzylation reaction was applied on chrysin to protect hydroxyl phenol moiety. Then, halogenation by iodine or bromine in anhydrous acetic acid was performed to obtain halogenated chrysin. Finally, intermediate compounds were treated with areneboronic derivatives catalyzed by palladium tetrakits to generate arylchrysin analogues with high yields.
Key words: arylchrysin, carbon-carbon coupling Suzuki reaction.

INTRODUCTION

Chrysin (5,7-dihydroxyflavone), a naturally wide distributed flavonoid, has been reported to have many different biological activities such as anti-inflammatory**,** anti-oxidant, anti-allergy and anti-cancer activity[1-2]... For the anti-inflammatory effect, it has been showed that chrysin acts as an agonist of PPAR-γ which results in down-regulation of the key pro-inflammatory enzymes, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2, prostaglandin synthase)[3-4]. Furthermore, some chrysin derivatives such as wogonin (8-methoxychrysin), and baicalein (6-hydroxychrysin), Oroxylin A (6-methoychrysin) (**Figure 1**), found in the nature have demonstrated their inhibition of PGE_2 production stronger than those of chrysin.[5-6] The primary SAR of compounds show that, the substitution of either position 6 or position 8 on A ring of chrysin may be contribute to their activity of inhibition of PGE_2 production[7].

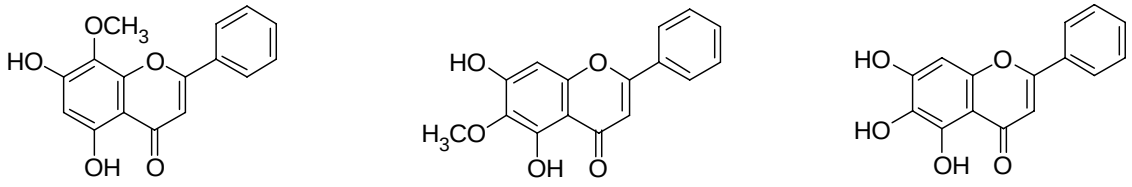


Figure 1: Structure of some natural chrysin derivatives.

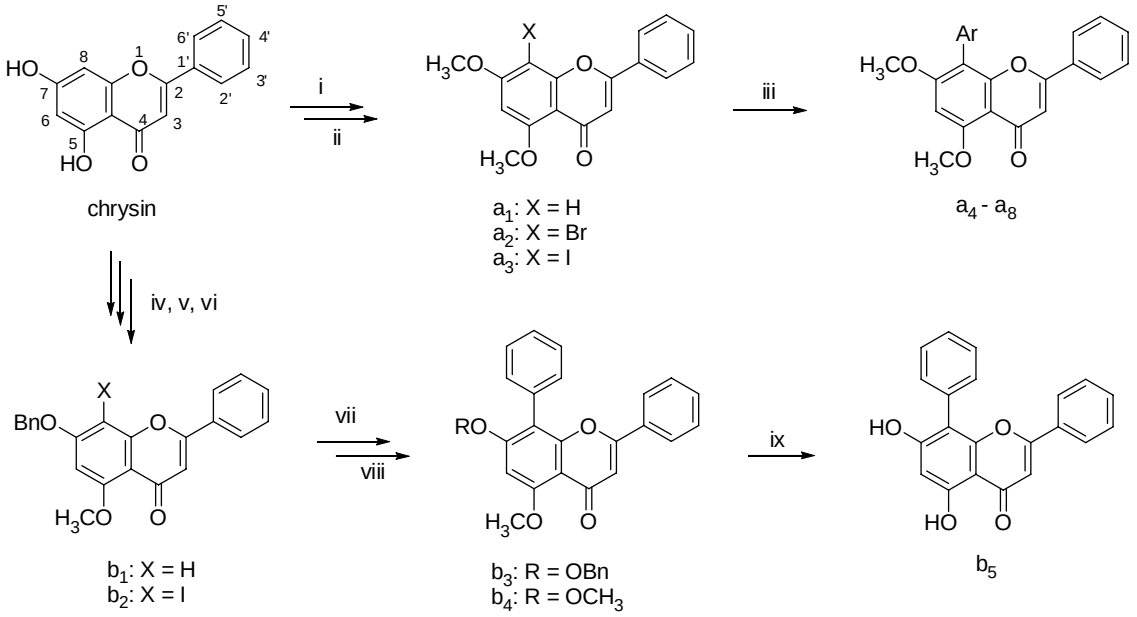
From the knowledge, the aryl groups attached into the ring system of flavone contribute the enhancement of lipophile characteristics comparable to the polyhydroxyflavone. It may be lead to increase the *in vivo* bioactivity of chrysin because of their permeability through the skin and other biological membranes.
To obtain some new flavone supporting for process of screening biological activities some arylchrysin analogues were synthesized and determined their physic-chemical characteristic.
Herein, we report the processes for synthesis of some arylchrysin derivatives by Suzuki reaction[8] via 8-iodochrysin or 8-bromochrysin as starting materials.

MATERIALS AND METHODS

All chemicals were obtained from commercial suppliers, and used without further purification. All solvents used for reaction were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^{1}H-NMR spectra were recorded on a Varian 200 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet) and dd (doublet of doublets). Analytical thin-layer chromatography (TLC) was performed using commercial glass plate with silica gel 60F254 purchased from Merck. Chromatographic purification was carried out by flash column chromatography using Kieselgel 60 (230-400 mesh, Merck).

All 8-arylchrysin analogues were synthesized by the carbon-carbon coupling Suzuki reaction from intermediate halogenated chrysin and areneboronic derivatives, followed the process of deprotection by c-HCl acetic acid or BBr_3 in refluxed chloroform to give the free hydroxyl arylchrysin derivatives (Scheme 1.).

The synthetic compounds were crystallized twice from methanol or mixture of dichloromethane and methanol (1:1). The title compounds were determined their melting point, thin layer chromatography and ^{1}H-NMR.



Scheme 1. Synthetic routes for arylchrysin analogues

i: dimethyl sulfate, K_2CO_3, acetone, refluxed; ii: Oxone®, NaX (Br, I), acetone-H2O, 0 ^oC; iii: areneboronic derivatives, DMF, $Pd(PPh_3)_4$, refluxed; iv: BnBr, K_2CO_3, acetone, refluxed; v: dimethyl sulfate, K_2CO_3, acetone, refluxed; vi: iodine, acetic acid, rt; vii: phenylboronic acid, DMF, refluxed; viii: c-HCl/acetic acid, ref.; ix: BBr_3, $CHCl_3$, refluxed.

RESULTS AND DISCUSSION

8-Halogeno-5,7-*O*-dimethylchrysin (**a$_2$**, **a$_3$**) key intermediate for synthesis of 8-arylchrysin

analogues, was prepared from commercially available chrysin in two steps. First, reaction of chrysin with dimethyl sulfate (2.2 equiv) and potassium carbonate in anhydrous acetone solution at refluxing condition afforded 5,7-*O*-dimethylchrysin. And finally, reaction of this obtained compound in anhydrous acetic acid and iodine or bromine in dried acetone gave the corresponding 8-halogeno-5,7-*O*-dimethylchrysin (**a_2** and **a_3**).

For synthesis of 8-arylchrysin, we carried out a different synthetic pathway. First, treatment of chrysin with benzyl bromide in dried acetone catalyzed by K_2CO_3 under reflux condition to obtain 7-*O*-benzylchrysin. This compound was treated further with dimethyl disulfate as the same above mentioned conditions gave 5-*O*-methyl-7-*O*-benzylchrysin (**b_1**). After all, reaction of this compound in acetic acid with iodine or bromine gave 8-halogeno-5-*O*-methyl-7-*O*-benzylchrysin (**b_2**).

Suzuki reaction conditions were applied to introduce an aryl group to the A ring system of chrysin. The coupling reaction of the 8-halogenochrysin and areneboronic acid in the presence of small amount of $Pd(PPh_3)_4$ in anhydrous dimethyl formamide gave 8-arylchrysin analogues (**a_4- a_8** and **b_3**) as shown in Scheme 1.

Hydrolysis of the compound **b_3** in c-HCl/acetic acid under reflux condition gave the 5-*O*-methyl-7-hydroxy-8-phenylchrysin **b_4**. Treatment of **b_4** with BBr_3 in dried chloroform under reflux condition obtained 8-phenyl-5,7-*O*-dimethylchrysin **b_5** as showed in Scheme 1.

Table 1. Structure of synthetic arylated chrysin derivatives

No.	Name	Substituents at A ring				Yield
		C_5	C_6	C_7	C_8	%
a_4	8-phenyl-5,7-*O*-dimethylchrysin	OMe	H	OMe	$-C_6H_5$	62[a] – 68[b]
a_5	8-(3,4-dimethoxyphenyl)-5,7-*O*-dimethylchrysin	OMe	H	OMe	$-C_6H_3(3',4'-OCH_3)_2$	63[a] – 71[b]
a_6	8-(3,4,5-trimethoxyphenyl)-5,7-*O*-dimethylchrysin	OMe	H	OMe	$-C_6H_2(3',4',5'-OCH_3)_3$	65[a] – 70[b]
a_7	8-(3-formylphenyl)-5,7-*O*-dimethylchrysin	OMe	H	OMe	$-C_6H_4(3'-CHO)$	68[a] – 75[b]
a_8	8-(4-formylphenyl)-5,7-*O*-dimethylchrysin	OMe	H	OMe	$-C_6H_4(4'-CHO)$	74[a] – 80[b]
b_3	8-phenyl-5-*O*-methyl-7-*O*-benzylchrysin	OMe	H	OBn	$-C_6H_5$	65[a] – 68[b]
b_4	8-phenyl-5-*O*-methylchrysin	OMe	H	OH	$-C_6H_5$	61[a] – 65[b]
b_5	8-phenylchrysin	OH	H	OH	$-C_6H_5$	55[a] – 58[b]

[a]*: yield % obtained with bromochrysin derivatives*
[b]*: yield % obtained with bromochrysin derivatives*

Synthesis of halogenated chrysin as intermediate reagents

5,7-*O*-Dimethylchrysin (a_1): chrysin (7.5 mmol), K_2CO_3 (30 mmol) and dimethyl sulfate (15 mmol) in 20 mL of acetone were refluxed for 4-6hrs, monitoring by TLC using mixture of chloroform and methanol (20:1) as developmental solvent. After removing potassium carbonate, the reaction solution was poured into a beaker containing 100 mL of water. Solid was filtered, washed with water, dried and crystallized from methanol to yield colorless solid with overall yield 90 %. Mp: 132 ^oC. ^1H-NMR (200 MHz, $CDCl_3$): δ 7,75-7,98 (d, 2H, *J* =

8,2 Hz, H2', H6'), 7.49-7.53 (m, 3H, H3', H4', H5'), 6.69 (s, 1H, H3), 6,39 (ds, 1H, J = 2,2Hz, H8); 3.97-3.92 (s, 6H, 2xOCH_3).

8-Bromo-5,7-*O*-dimethylchrysin (a_2): to the mixture of bromine (3.2 g, 20 mmole), **a_1** (5.65 g, 20 mmole) in 40 mL of glacial acetic acid stirring in ice bath for 30 minutes was slowly added 2 g of 65% HNO_3 acid diluted in 10 mL of acetic acid. The product was precipitated during the addition. The reaction mixture was stirred for two hours more and diluted with 40 mL of cold water. The solid was filtered and washed with 10 % $Na_2S_2O_4$ solution, and water. The residue was crystallized from methanol to give the title compound as a pale yellow solid (yield 85 %). ^{1}H-NMR ($CDCl_3$/200MHz, δppm): 8.00 (d, 2H, $H_{2'}$-$H_{6'}$), 7.54-7.52 (t, 3H, $H_{3'}$-$H_{4'}$-$H_{5'}$), 6.73 (s, 1 H, H_6), 6.47 (s, 1H, H_8), 4.05-4.03 (d, 6H, OCH_3).

8-Iodo-5,7-dimethoxyflavone (a_3): the product was obtained as pale yellow solid (yield 70 %) according to the same procedure as preparation of **a_2**, using iodine (5.07 g, 20 mmol) as reagent for halogenation. ^{1}H-NMR ($CDCl_3$/200MHz, δppm): d 8.05-8.09 (d, 2H, H2', H6'), 7.52-7.55 (m, 3H, H3', H4', H5'), 6.75 (s, 1H, H6), 6.45 (s, 1H, H_3), 4.04 (s, 6H, 2xOCH_3).

7-Benzyloxy-5-methoxyflavone (b_1): selective benzyl protection at the phenol at 7-position was carried out with chrysin, K_2CO_3 and benzyl chloride (1 equiv.) in acetone. Further methyl protection of the intermediate reactant with dimethyl sulfate (1.1 equiv.) gave the title product (b_1) with yield 72%. ^{1}H-NMR ($CDCl_3$/200MHz, δppm): 7.85-7.90 (d, 2H, H2', H6'), 7.40-7.53 (m, 8H, H3', H4', H5', phenyl), 6.70 (s, 1H, H6), 6.66 (S, 1H, H3), 6.47 (s, 1H, H3), 5.17 (s, 2H, -CH2), 3.96 (s, 3H, OCH_3).

7-Benzyloxy-8-iodo-5-methoxyflavone (b_2): iodination of the compound **b_1** was followed the procedure for the compound **a_3**. Yield 65 %. ^{1}H-NMR ($CDCl_3$/200MHz, δppm): 8.04-8.09 (d, 2H, H2', H6'), 7.40-7.55 (m, 8H, H3', H4', H5', phenyl), 6.73 (s, 1H, H6), 6.47 (S, 1H, H3), 5.32 (s, 2H, -CH2), 3.96 (s, 3H, OCH_3).

Synthesis of compounds a_4- a_8 and b_3

Briefly, to a solution of 8-halogenchrysin analogues (**a_2/a_3/b_2**, 3.5 mmol) and areneboronic acid derivatives (6 mmol) in 20 mL of dried dimethoxyethane was added $Pd(PPh_3)_4$ (0.2 mmol). The resulting mixture was degassed and stirred at ambient temperature for 20 minutes before adding saturated aqueous Na_2CO_3 solution (10 mL). The mixture was degassed again and then stirred under nitrogen gas for 1 h. The additional areneboronic acid (10 mmol) then added, and the reaction mixture was heated at 80 ^{o}C for 4 hrs. After cooling to room temperature, the mixture was diluted with dichloromethane (40 mL) and water (20 mL), the organic phase was separated, washed with water and dried over magnesium sulfate, filtered and evaporated in reduced pressure. The residue was purified by flash column to obtain the corresponding 8-arylchrysin analogues (**a_4- a_8 and b_3,** displayed in Table 1).

8-phenyl-5,7-*O*-dimethylchrysin (a_4)
M.p 167-169 ^{o}C. ^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 8.04-8.08 (d, 2H, H2', H6'), 7.50-7.54 (m, 5H, phenyl), 7.16-7.20 (m, 3H, H3', H4', H5'), 6.74 (s, 1H, H6), 6.45 (s, 1H, H3), 4.03 (s, 6H, 2xOCH_3);.

8-(3,4-dimethoxy-phenyl)-5,7-*O*-dimethylchrysin (a_5)
M.p. 201-204 ^{o}C. ^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 7.35-7.659 (m, 5H, H2', H3', H4', H5', H6'), 7.0 (s, 1H, C2''), 6.74-6.98 (d, 2H, H5'', H6''), 6.72 (s, 1H, H6), 6.53 (s, 1H, H3), 4.07 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3).

8-(3,4,5-trimethoxyphenyl)-5,7-*O*-dimethylchrysin (a_6)
M.p. 245-247 ^oC. ^1H-NMR (200 MHz, $CDCl_3$, δ ppm): 7.35-7.59 (m, 5H, H2', H3', H4', H5', H6)', 6.72 (s, 1H, H6), 6.65 (s, 2H, H2", H6"), 6.53 (s, 1H, H3), 4.07 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.85 (s, 6H, 2xOCH_3).

8-(3-formylphenyl)-5,7-*O*-dimethylchrysin (a_7)
M.p. 220-222 ^oC. ^1H-NMR (200 MHz, $CDCl_3$, δ ppm): 10.1 (s, 1H, CHO), 7.30-8.0 (m, 9H, H2', H3', H4', H5', H6', H2", H4", H5", H6"), 6.70 (s, 1H, H3), 6.54 (s, 1H, H6), 4.08 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3).

8-(4-formylphenyl)-5,7-*O*-Dimethylchrysin (a_8)
M.p. 244-246 ^oC. ^1H-NMR (200 MHz, $CDCl_3$, δ ppm): 10.13 (s, 1H, CHO), 8.00 - 8.04 (d, 2H, J = 8 Hz, J = 2 Hz, H2', H6'), 7.16-7.63 (m, 7H, H3', H4', H5', H2", H3", H5", H6"), 6.70 (s, 1H, H3), 6.54 (S, 1H, H6), 4.09 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3).

8-phenyl-7-*O*-benzyl-5-*O*-methylchrysin (b_3)
M.p. 188-191 ^oC. ^1H-NMR (200 MHz, $CDCl_3$, δ ppm): 7.29-7.53 (m, 10H, H2', H3', H4', H5', H6', H2", H3", H4", H5", H6"), 6.70 (s, 1H, H6), 6.55 (s, 1H, H3), 5.20 (s, 2H, -CH_2), 3.97 (s, 3H, OCH_3).

8-phenyl-5-*O*-methylchrysin (b_4)
The compound **b_3** was refluxed with acid c-HCl in acetic acid for 6 hrs (monitoring by TLC). Further, the mixture was diluted with dichloromethane and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under the reduced pressure. The residue was crystallized from chloroform-methanol to obtain the compound **b_4** (see Table 1).
M.p 194-196 ^oC. ^1H-NMR (200 MHz, DMSO-d_6, δ ppm): 13.03 (bs, 1H, OH), 10.95 (s, 1H, OH), 7.41-8.10 (m, 10H, H2', H3', H4', H5', H6', phenyl), 7.14 (s, 1H, H6), 6.45 (s, 1H, H3);

8-phenylchrysin (b_5)
To a solution of **b_4** (8 mmol) in 20 mL of dry chloroform was added BBr_3 diluted in CH_2Cl_2 (24 mmole), and the reaction mixture was stirred at refluxing condition for over-night. The reaction mixture was cooled to room temperature and was added methanol to decompose the excess BBr_3. After evaporation in vacuum, the residue was dissolved in aqueous 1N NaOH solution and washed two times with ethyl acetate. The solution was cooled to 0 ^oC and acidified to pH = 3 by using 3M HCl solution. The precipitated solid was filtered and recrystallized from methanol to get the titled compound (Table 1).
M.p. 296-298 ^oC (decompose). ^1H-NMR (200 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 9.88 (s, 1H, OH), 7.38-7.55 (m, 10H, H2', H3', H4', H5', H6', H2", H3", H4", H5", H6"), 6.64 (s, 2H, H3, H6), 3.97 (s, 3H, OCH_3).

CONCLUSIONS

The reaction of halogenchrysin and areneboronic acid based on the Suzuki carbon-carbon coupling conditions afforded the corresponding arylchrysin analogs in a three to five steps domino reaction. The iodochrysin derivatives used as starting materials gave higher yield than that of the corresponding bromochrysin derivatives. However, halogenation of chrysin derivatives by bromine reagent are more convenient and higher yield than those of the iodine reagent.

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