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Research Article

SYNTHESIS OF 6-(HETERYL/ARYL) CHROMONES

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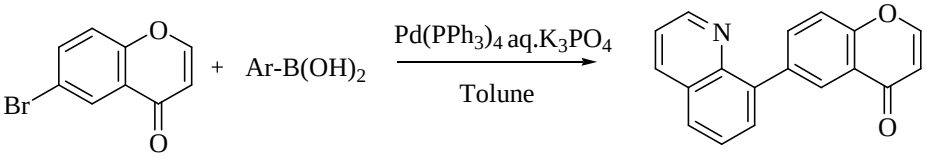


ABSTRACT

New series of hetroannulated 6-(heteryl/aryl)chromones **(3a-g)** from the Suzuki coupling reaction of 6-Bromochromones**(2)** react with heteryl and aryl boronic acids (**2a-g)** in $Pd(PPh_3)_4$ under catalyst K_3PO_4 in good yields.

Keywords: 6-Bromochromones, Pd $(PPh_3)_4$, K_3PO_4, Heteryl and aryl-boronic acids, PPA. Suzuki reaction.

INTRODUCTION

Natural products are typically secondary metabolites, produced by organisms in response to external stimuli such as nutritional changes, infection and competition. Natural products produced by plants, fungi, bacteria, insects and animals have been isolated as biologically active pharmacophores. Approximately one-third of the top-selling drugs in the world is natural products or their derivatives often with ethnoharmacological background. Moreover, natural products are widely recognized in the pharmaceutical industry for their broad structural diversity as well as their wide range of pharmacological activities.

Coumarin constitutes one of the major classes of naturally occurring compounds, and interest in its chemistry continues unabated because of its usefulness as biologically active agents. It also represents the core structure of several molecules of pharmaceutical importance. Chromones and isoflavones with medicinal use are Khellin a coronary vasodilator.Coumarin has been reported to serve as anti-oxidant, antibacterial and antitumour agents. These pharmacological properties of coumarin aroused our interest in synthesizing some coumarin derivatives with the aim of testing their microbiological activity. Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitising, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity. The usefulness of coumarins and coumarin derivatives has been shown in various areas of analysis. The inherent fluorescent properties of many coumarins are a key factor in many applications. Areas herecoumarins are widely used include estimation of enzymatic activity. It is used inelectroplating to reduce the porosity and increase the brightness of various deposits, such as nickel.6-methylcoumarin is mainly used as a flavour enhancer, and 7-hydroxycoumarin in sunscreens.

The Suzuki cross-coupling reaction is the palladium catalyzed C-C bond formation reaction of organoboron compounds with organic halides or pseudo halides. The synthesis of boronic acids which are based on the reaction of trialkyl borates with Grignard or organolithium reagents. The classical synthesis of alkenylboronic acids or their esters from Grignard reagents or lithium reagents and trialkyl borates is an efficient method for making relatively simple boron compounds in large quantities.

EXELERIMENTAL SECTION

General: Melting points were determined on a Polmon instrument (model no. MP-96).IR spectra were recorded on Perkin-Elmer 337 spectrometer, and ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) were recorded on a VarianGemini 200 spectrometer using TMS as internal standard (chemical shifts values were described in ppm δ). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass LCMS 2010 instrument.

General procedure for the synthesis of 6-(heteryl/aryl) chromones (3a-g)

6-Bromochromone **(1)** (0.2g, 0.8 mmol, leq) was stirred in the presence of 4 mol% of tetrakis (triphenylphosphine) palladium at room temperature under nitrogen for 30 min, toluene (5 mL) and K_3PO_4 (1 mL of 2 mol dm^{-3} aqueous solution). 8-quinoline boronic acid **(2a)** (0.17g, l.0mmol, 1.3 equiv) in toluene was added and the mixture was stirred for 30 min. The reaction mixture was heated under reflux for 12 hours, after completion of the reaction, it was cooled to room temperature and diluted with chloroform (50mL), washed with water (3 x 20 mL). The aqueous layers were combined and further extracted with chloroform (3 x 30 mL). The organic extracts were combined, dried over Na_2SO_4 and the solvent evaporated. The residue was purified by column chromatography using ethyl acetate and pet ether to give 6-(8-quinolyl) chromone **(3a)** (0.13g, yield 58%), white solid.mp 120 °C.

IR (KBr): 1695cm^{-1} (C=O).

^{1}H NMR ($CDC1_3$.400MHz): δ 8.92 (dd, J=4.0Hz, J=2.0Hz, H-2'), 8.21 (d, J=2.0Hz, H-5), 8.18 (dd, J=8.0Hz, J=2.0Hz, H-4'), 7.90 (dd, J=8.4Hz, J=2.9Hz, H-5'), 7.80 (dd, J=8.0 Hz, J=2.0Hz, H-7), 7.71 (dd, J=7.2Hz, J=1.6Hz, H-7'), 7.57 (dd, J=7.2Hz, J=7.2Hz, H-3'), 7.39 (dd, J=8.4Hz, J=4.4Hz, H-6'), 7.10 (d, J=8.0Hz, H-8), 4.58 (t, J=6.4Hz, OCH), 2.84 (t, J=6.4Hz, 3-CH).

^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 191,1 (C=O), 161.3 (C-8a), 150.1 (C-2'), 146.0 (C-8'a), 139.4 (C-6), 138.5 (C-7), 136.1 (C-4'), 132.9 (C-8'), 129.8 (C-7'), 128.8 (C-5), 127.6 (C- 5'), 126.2 (C-3'), 124.7 (C-4'a), 121.4 (C-4a), 121.1 (C-7), 117.2 (C-8), 67.0 (C-2), 37.9 (C-3).

DIPMS: m/z 276[M+H].

Employing the similar procedure as mentioned for **3a**, compounds **3b-g** were obtained from **2b-g** as solids.

***ii) 6-(2-Methyl-4-pyridyl) chromone* (3b)**

Light yellow solid, mp 107 °C, yield 48%.

IR (KBr): 1695cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 400MHz): δ 8.52 (d, J=5.2Hz, H-6'), 8.18 (d, J=2.4Hz, H-5), 7.76 (dd, J=8.4Hz, J= 2.4Hz, H-7), 7.54 (m, H-5'), 7.29 (d, J=2.0Hz, H-3'), 7.10 (d, J=8.4Hz, H-8), 4.60 (t, J=6.4Hz, OCH), 2.86 (t, J=6.4Hz, 3-CH), 2.61 (s, 2'-CH_3).

^{13}C NMR ($CDC1_3$,100.6 MHz): δ 191.4 (C=O), 162.3 (C-8a), 159.0 (C-2'), 149.6 (C-6'), 147.0 (C-6), 134.0 (C-4'), 132.0 (C-7), 131.7 (C-3'), 128.4 (C-5), 125.4 (C-5'), 120.4 (C- 4a), 118.7 (C-8), 67.1 (C-2), 37.6 (C-3), 24.2 (C-2'-CH_3).

DIPMS: m/z 240[M+H].

***iii) 6-(6-Chloro-3-pyridyl) chromone* (3c)**

White solid mp 137 ^{o}C, yield 58%.

IR (KBr): 1695cm^{-1} (C=O).

^{1}H NMR ($CDC1_3$, 400MHz): δ 8.57 (d, J=2.0Hz, H-6'), 8.08 (s, H-5), 7.84 (dd, J=8.0Hz, J= 2.4Hz, H-7), 7.68 (dd, J=8.0Hz, J=2.4Hz, H-3'), 7.40 (d, J=8.4Hz, H-7), 7.10 (d, J=8.4Hz, H-8), 4.60 (t, J=6.4Hz, OCH), 2.87 (t, J=6.4Hz, 3-CH).

^{13}C NMR ($CDC1_3$,100.6 MHz): δ 191.0 (C=O), 162.2 (C-8a), 147.6 (C-6'), 147.4 (C-2'), 137.6 (C-5'), 136.7 (C-7), 136.5 (C-4'), 134.0 (C-7), 126.3 (C-5), 125.3 (C-3'), 121.9 (C- 4a), 119.1 (C-8), 67.3 (C-2), 37.8 (C-3).

DEPMS: m/z 260[M+H], 262[M+H+2].

***iv) 6-(5-Methyl-2-furyl) chromone* (3d)**

Yellow solid, mp 87 ^{o}C, yield 52%.

IR (KBr): 1695cm^{-1} (C=O).

^{1}H NMR ($CDC1_3$, 400MHz): δ 8.08 (d, J=2.0Hz, H-5), 6.98 (d, J=8.8Hz, H-7), 6.89 (d, J=8.8Hz, H-8), 6.50(d, J=3.0Hz, H-3'), 6.05(d, J=3.0Hz, H-4'), 4.54 (t, J=6.4Hz, OCH), 2.81 (t, J=6.4Hz, 3-CH), 2.36 (s, 5'-CH_3).

^{13}C NMR ($CDC1_3$,100.6MHz): δ 191.0 (C=O), 160.7 (C-8a), 151.8 (C-2'), 151.2 (C-5'), 138.4 (C-7), 131.1 (C-5), 125.5 (C-4a), 121.6 (C-8), 118.0 (C-6), 107.6(C-3'), 105.5(C- 4'), 67.0 (C-2), 37.8 (C-3), 13.3 (C5'-CH_3).

DIPMS: m/z 229[M+H].

***v) 6-(3,4-Dimethyl-phenyl) chromone* (3e)**

White solid, mp 97 ^{o}C, yield 44%.

IR (KBr): 1695 cm^{-1} (C=O).

^{1}H NMR ($CDC1_3$, 400MHz): δ 8.10 (d, J=2.4Hz, H-5), 7.68 (dd, J=8.8Hz, J=2.4HZ, H-7), 7.34 (s, 2'-H), 7.29 (d, J=8.0Hz, H-6'), 7.16 (d, J=8.0Hz, H-5'), 7.0 (d, J=8.8Hz, H-8), 4.52 (t, J=6.4Hz, OCH), 2.81 (t, J=6.4Hz, 3-CH), 2.30 (s, CH_3), 2.27 (s, CH_3).

^{13}C NMR (100.6 MHz, $CDC1_3$): δ 191.1 (C=O), 161.0 (C-8a), 137.3 (C-3'), 136.8 (C-6), 135.5 (C-4'), 134.8 (C-7), 134.2 (C-2'), 130.0 (C-1'), 127.9 (C-5'), 124.8 (C-6'), 124.0 (C-5), 121.5 (C-4a), 118.0 (C-8), 67.0 (C-2), 37.8 (C-3), 19.4 (C-4'-CH_3), 18.9 (C-3'-CH_3).

DIPMS: m/z 253[M+H].

***vi) 6-(2,3-Difluorophenyl) chromone* (3f)**

White solid, mp 112 ^{o}C, yield 51 %.

IR (KBr): 1695cm^{-1} (C=O).

^{1}H NMR ($CDC1_3$, 400MHz): δ 8.07 (d, J=1.2Hz, H-5), 7.68 (dd, J=8.4Hz, J=1.2Hz, H-7), 7.17-7.10 (m, H-4', 5', 6'), 7.05 (d, J=8.4Hz, H-8), 4.58 (t, J=6.4Hz, OCH), 2.85 (t, J=6.4Hz, 3-CH).

^{13}C NMR ($CDC1_3$, 100.6 MHz): δ 190.6 (C=O), 161.6 (C-8a), 152.4 (C-2'), 136.1 (C-3'), 129.9 (C-6), 128.1 (C-7), 127.3 (C-6'), 124.9 (C-l'), 124.0 (C-5), 121.4 (C-4'), 118.1 (C-4a), 116.1 (C-4'), 115.9 (C-8), 67.1 (C-2), 37.7 (C-3).

DIPMS: m/z 261[M+H].

***vii) 6-(2-Fluorophenyl)-4-chromone* (3g)**

White solid, mp 69 ^{o}C, yield 56%.

IR (KBr): 1695 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 400MHz): δ 8.10 (d, J=1.2Hz, H-5), 7.71 (dd, J=8.8Hz, J=2.0Hz, H-6'), 7.44 (dd, J=7.6Hz, J=1.6Hz, H-7), 7.29 (m, 3'-H), 7.21-7.11 (m, H-3',4'), 7.04 (d, J=8.4Hz, H-8), 4.57 (t, J=6.4Hz, OCH), 2.84 (t, J=6.4Hz, 3-CH).

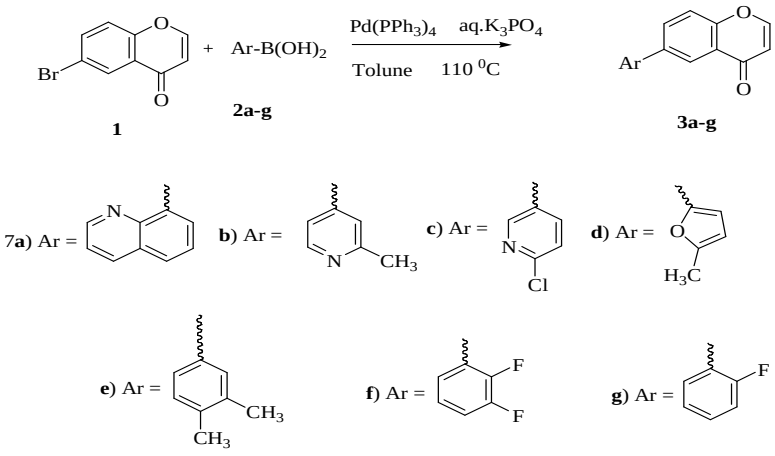
^{13}C NMR ($CDC1_3$, 100.6 MHz): δ 191.0 (C=O), 161.3 (C-8a), 136.4 (C-2'), 130.3 (C-6),129.2 (C-l'), 129.0 (C-l'), 128.9 (C-6'), 127.3 (C-4'), 124.3 (C-5), 121.3 (C-5'), 117.9 (C-4a), 67.2 (C-2), 37.6 (C-3).

DIPMS: m/z 243[M+H].

RESULTS AND DISCUSSION

Equimolar amount of 6-bromochromone **(1)** on reaction with heteryl and aryl-boronic acids **(2a)** in presence of Pd (PPh_3)$_4$, K_3PO_4 in toulene at refluxing to give 6-(8-quinolyl) chromone **(3a)**. The IR spectrum of 6-(8-quinolyl) chromone **(3a)**, the carbonyl group showed peak at 1695 cm^{-1}. In the ^{1}H-NMR ($CDCl_3$, 400MHz) spectrum, the quinoline protons appeared at δ 8.92 (dd, J=4.0Hz, J=2.0Hz, H-2'), 8.18 (dd, J=8.0Hz, J= 2.0Hz, H-4'), 7.90 (dd, J=8.4Hz, J=2.0Hz, H-5'), 7.71 (dd, J= 7.2Hz, J =1.6Hz, H-7'), 7.57 (dd, J=8.0Hz, J=8.0Hz, H-6'), 7.39 (J =8.4Hz, J= 4.0Hz, H-3'). The chromone protons appeared at δ 8.21 (d, J=2.0Hz, H-5), 7.80(dd, J=8.0Hz, J=2.0Hz, H-7), 7.10 (d, J=8.0Hz, H-8), δ 4.58 (t, J=6,4Hz, OCH_2), 2.84 (t, J=6.4Hz, $COCH_2$). In the ^{13}C-NMR ($CDC1_3$, 100.6MHz) the quinoline carbons appeared as follows: δ 150.1 (C-2'), 146.0 (C-8'a),136.1 (C-4'), 132.9 (C-8'), 129.8 (C-7'),124.7 (C-4'a),126.2 (C-3'),127.6 (C-5'), and the chromone carbon assignment are δ191.1 (CO), 161.3 (C-8a), 139.4 (C-6), 138.5 (C-7), 128.8 (C-5), 121.4 (C-4a), 121.1 (C-7), 117.2 (C-8), 67.0 (C-2), 37.9 (C-3).

In the DIPMS spectrum of 6-(8-quinolyl) chromone **(3a)** quasimolecular ion peak observed at m/z 276[M+H].



Scheme 1

CONCLUSION

We have developed a mild method for the synthesis of seven new 6-(8-quinolyl) chromone derivatives from readily available 6-Bromochromone *via* K_3PO_4 catalyzed reaction. Also, the required key starting materials (i.e., 6-Bromochromone) have been synthesized by use of *Suzuki coupling reaction*. This newly established method useful for the preparation of biologically active hetroannulated 6-(8-quinolyl) chromone derivatives.

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