

Synthesis of Carbohydrate-Conjugated Flavone Derivatives

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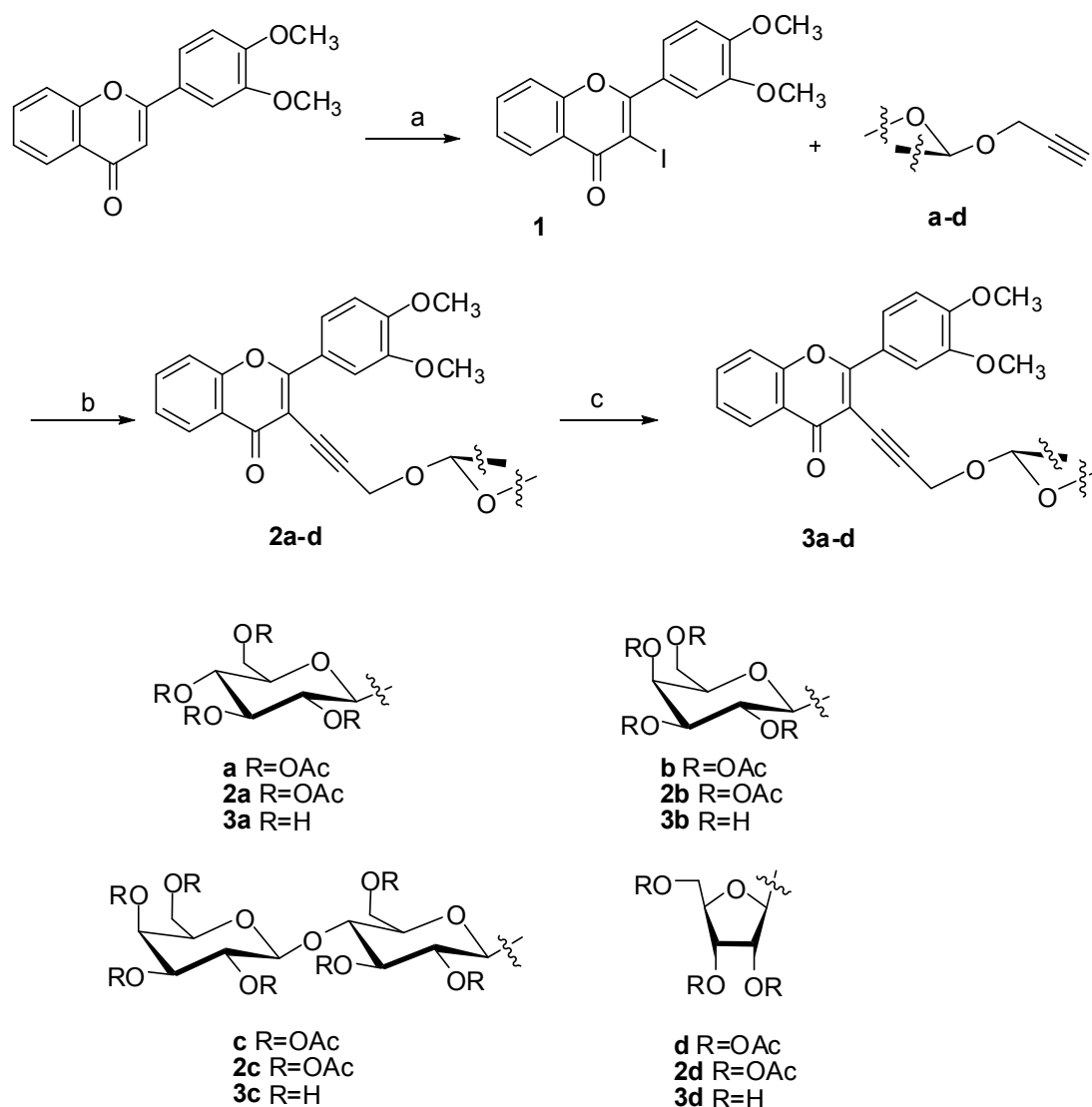
Abstract. A series of flavone derivatives conjugated with carbohydrate were synthesized from 2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one. The key step is its cross coupling with the carbohydrate under Sonogashira reaction.

Introduction

Aryl glycosides, and especially flavone *O*-glycosides are of considerable interest because of their widespread occurrence in nature [1,2] as well as their profound biological activities [3]. In our continuous research for discovering antitumor molecules, we have recently reported the synthesis of various carbohydrate-conjugated nucleoside e.g. 5-(carbohydrate-ethynyl)-2'-deoxyuridine [4], carbohydrate-conjugated dT analogues [5], carbohydrate-conjugated furo[2,3-*d*]pyrimidine [6]. In further pursue of our research, we became interested in the synthesis of a combinatorial library based on the scaffold of flavones, especially 3-carbohydrate-conjugated flavones for their *in vitro* assay against various cancer cell lines.

Results and Discussion

Although there are many positions for the introduction of diversity into flavone skeleton (as shown in Scheme 1), in present paper, we focused on the modification of C-3. We postulated that attachment of an alkynyl-carbohydrate moiety at the C-3 position of flavone ring might lead to a novel class of compounds, which have potentially biological significance. In present paper, we tried to synthesize a new series of flavone derivatives conjugated with carbohydrate by the Sonogashira reaction to improve their aqueous solubility and the possible antiviral activities. Initially, 3-iodo-flavone (**1**) was synthesized from 2-(3,4-dimethoxyphenyl)-4*H*-chromen-4-one in 89% yield in CAN facilitated iodination. Analytically pure **1** was obtained by simple filtration, which can be used without further purification. Treatment of **1** with propargyl carbohydrates **a-d** under Sonogashira conditions [5% Pd(PPh₃)₄, 10% CuI, DMF] at 80 °C afforded the flavone analogue **2a-d**. In the last deprotection step, all acetyl groups were easily removed in a saturate solution of NH₃ in MeOH. After column chromatography, the target molecules **3a-d** were obtained in moderate yields. Their structures were confirmed by various spectroscopies.



Reagents and conditions: a) MeCN, I₂, (NH₄)₂Ce(NO₃)₆, 65 °C, Ar, 10h, 89%; b) 5% Pd(PPh₃)₄, 10% CuI, DMF, 80 °C ; c) saturated NH₃ in MeOH, r.t., 12h, 75-83%.

Scheme 1 Synthesis of carbohydrate-conjugated flavone derivatives

Experimental section

Apparatus and reagents. All solvents were dried and distilled prior to use according to the standard methods. Commercially available chemicals were used as received. NMR spectra were recorded on Bruker AV400 (400 MHz) spectrometer and chemical shifts (δ) are given in ppm. ¹H-NMR and ¹³C-NMR spectra were recorded with TMS as internal standard and coupling constants (J) are given in Hz. The ESI-HRMS were measured on a Bruker APEX II spectrometer in positive and negative ion mode.

Synthetic route. The synthesis route of compound **3a-d** see scheme 1.

General procedure for the preparation of 3-iodo-flavone **1**. A mixture of flavone (0.294 g, 1.0 mmol), iodine (0.279 g, 1.10 mmol) and ceric ammonium nitrate (0.548 g, 1.0 mmol) in acetonitrile (20 mL) was stirred at 65 °C under Ar atmosphere for 5 h. The mixture was then poured into water (50 mL), extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with cold sodium thiosulfate solution (2 × 10 mL), water (2 × 30 mL) and dried over Na₂SO₄. The solvent was concentrated under reduced pressure and analytically pure **1** was obtained, which can be used without further purification.

General procedure for the synthesis of compounds **2a-d**. In a typical reaction, CuI (0.2 mmol) and triethylamine (3 mmol) were added to a degassed solution of **1** (590 mg, 1.0 mmol) and **a-d** (1.5 mmol) in anhydrous DMF (5 mL). After the reaction mixture was stirred for 10 minutes, freshly prepared Pd(PPh₃)₄ (0.1 mmol) was added in one portion. The solution was stirred under a Ar atmosphere at room temperature overnight. DMF was removed under high vacuum and the residue was purified by silica gel column chromatography (ethyl acetate: petroleum ether = 2:3) to provide the desired **2a-d** as amorphous solid.

General procedure for the synthesis of compounds **3a-d**. A solution of one of **2a-d** (0.15 mmol) in a saturate solution of NH₃ (g) in MeOH (10 mL) was stirred at r.t. until the starting material was completely diminished. The reaction mixture was then concentrated to dryness and the residue was purified by flash column chromatography to give the corresponding compound **3a-d**.

3a: ¹H NMR (400 MHz, DMSO) δ: 8.04 (1H, d, H-5, *J* = 8 Hz), 7.83-7.73 (3H, m, H-2', 7, 6'), 7.72 (1H, d, H-8, *J* = 8 Hz), 7.49 (1H, t, H-6), 7.15 (1H, d, H-3', *J* = 8.4 Hz), 4.67, 4.56 (2H, dd, ArC≡CCH₂O), 4.31 (1H, H-1'', *J* = 8 Hz), 3.85, 3.84 (6H, s, OCH₃), 3.67 (1H, dd, H-6''a), 3.43 (1H, m, H-6''b), 2.98-3.18 (4H, m, H-2'', 3'', 4'', 5''); ¹³C NMR (100 MHz, DMSO) δ: 176.2 (C-4), 166.2 (C-2), 155.2 (C-8a), 152.3 (C-4'), 148.6 (C-3'), 135.1 (C-7), 126.23 (C-6), 125.4 (C-5), 124.0 (C-1'), 123.2 (C-6'), 121.8 (C-5a), 118.9 (C-8), 112.3 (C-2'), 111.8 (C-5'), 104.5 (C-3), 101.4 (C-1''), 94.5 (C≡CCH₂O), 79.3 (C≡CCH₂O), 77.4, 77.0, 73.6, 70.4 (C-2'', 3'', 4'', 5''), 61.5 (C-6''), 56.3, 56.2 (2OCH₃), 56.2 (C≡CCH₂O)

3b: ¹H NMR (400 MHz, DMSO) δ: 8.07 (1H, d, H-5, *J* = 8 Hz), 7.90-7.84 (3H, m, H-2', 7, 6'), 7.78 (1H, d, H-8, *J* = 8 Hz), 7.53 (1H, t, H-6), 7.21 (1H, d, H-3', *J* = 8.4 Hz), 4.64, 4.54 (2H, dd, ArC≡CCH₂O), 4.29 (1H, H-1'', *J* = 8 Hz), 3.88 (6H, s, OCH₃), 3.65 (1H, dd, H-6''a), 3.53 (1H, m, H-6''b), 3.53-3.17 (4H, m, H-2'', 3'', 4'', 5''); ¹³C NMR (100 MHz, DMSO) δ: 175.9 (C-4), 165.9 (C-2), 155.1 (C-8a), 152.1 (C-4'), 148.5 (C-3'), 134.8 (C-7), 126.1 (C-6), 125.3 (C-5), 123.9 (C-1'), 123.0 (C-6'), 121.6 (C-5a), 118.8 (C-8), 112.2 (C-2'), 111.7 (C-5'), 104.4 (C-3), 102.0 (C-1''), 94.5 (C≡CCH₂O), 79.0 (C≡CCH₂O), 75.7, 73.7, 70.6, 68.4 (C-2'', 3'', 4'', 5''), 60.8 (C-6''), 56.3, 56.2 (2OCH₃), 56.2 (C≡CCH₂O)

3c: ¹H NMR (400 MHz, DMSO) δ: 8.07 (1H, d, H-5, *J* = 8 Hz), 7.87-7.84 (3H, m, H-2', 7, 6'), 7.78 (1H, d, H-8, *J* = 8 Hz), 7.53 (1H, t, H-6), 7.20 (1H, d, H-3', *J* = 8.4 Hz), 4.72, 4.65 (2H, dd, ArC≡CCH₂O), 4.41 (1H, H-1''), 4.21 (1H, H-1'''), 3.88 (6H, s, OCH₃), 3.78, 3.62, 3.55-3.45, 3.34-3.29, 3.08 (12H, m, H-2'', 3'', 4'', 5'', 6'', 2'', 3'', 4'', 5'', 6''); ¹³C NMR (100 MHz, DMSO) δ: 176.1 (C-4), 166.3 (C-2), 155.3 (C-8a), 152.3 (C-4'), 148.7 (C-3'), 135.1 (C-7), 126.4 (C-6), 125.5 (C-5), 124.1 (C-1'), 123.2 (C-6'), 121.9 (C-5a), 119.0 (C-8), 112.4 (C-2'), 111.9 (C-5'), 104.6 (C-3), 104.3 (C-1''), 101.2 (C-1'''), 94.3 (C≡CCH₂O), 79.5 (C≡CCH₂O), 81.0, 76.0, 75.5*2, 73.7, 73.5, 71.0, 68.6 (C-2'', 3'', 4'', 5'', 2'', 3'', 4'', 5''), 61.0, 60.9 (C-6'', 6''), 56.3, 56.2 (2OCH₃), 56.4 (C≡CCH₂O)

3d: ¹H NMR (400 MHz, DMSO, δppm) δ: 8.07 (1H, d, H-5, *J* = 8 Hz), 7.88-7.84 (3H, m, H-2', 7, 6'), 7.78 (1H, d, H-8, *J* = 8 Hz), 7.52 (1H, t, H-6), 7.19 (1H, d, H-3', *J* = 8.4 Hz), 5.22 (1H, OH), 5.05 (1H, OH), 5.02 (1H, OH), 4.62, 4.53 (2H, dd, ArC≡CCH₂O), 4.32 (1H, H-1'', *J* = 8 Hz), 3.88 (6H, s, OCH₃), 3.71 (1H, dd, H-5''a), 3.29 (1H, m, H-5''b), 3.11-2.99 (3H, m, H-2'', 3'', 4''); ¹³C NMR (100 MHz, DMSO) δ: 176.1 (C-4), 166.2 (C-2), 155.3 (C-8a), 152.3 (C-4'), 148.7 (C-3'), 135.0 (C-7), 126.3 (C-6), 125.5 (C-5), 124.1 (C-1'), 123.2 (C-6'), 121.9 (C-5a), 119.0 (C-8), 112.4 (C-2'), 111.8 (C-5'), 104.6 (C-3), 102.3 (C-1''), 94.2 (C≡CCH₂O), 79.6 (C≡CCH₂O), 77.0, 73.6, 70.0 (C-2'', 3'', 4''), 66.2 (C-5''), 56.3, 56.2 (2OCH₃), 56.2 (C≡CCH₂O)

Summary

In conclusion, we have described a facile and mild palladium-mediated procedure for the synthesis of a series of carbohydrate-conjugated flavones under Sonogashira reaction condition. No significant side reaction such as dimerization of terminal alkynes or opening of the flavone ring was observed during the course of our reaction. Due to the operational simplicity as well as easy isolation and

purification procedures for the products the methodology appears to be a useful way to the flavone derivatives. Further research is ongoing in our laboratory and the evaluations of their biological activities are underway.

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References

- [1] J. Chopin, M. L. Bouillant, E. Besson in *The Flavonoids, Advances in Research* (J. B. Harborne, T. J. Mabry, Eds.), Chapman and Hall (1982), p. 449
- [2] K. M. Valant-Vetschera, *Bot. Rev.* Vol. 51 (1985), p. 1
- [3] T. Nagai, Y. Miyaichi, T. Tomimori, Y. Suzuki and H. Yamada: *Chem. Pharm. Bull.* Vol. 38 (1990), p. 1329
- [4] R.C. Yang, H.X. Ding, Y. Song, W.H. Xiao, Q. Xiao and Jun Wu, *Letters in Organic Chemistry*: Vol. 5 (2008), p. 518
- [5] X.Y. Jin, R.C. Yang, P.Y. Jin, Q. Xiao and Y. Ju, *Synthesis*: Vol. 19 (2007), p. 2967
- [6] X.Y. Jin, H.X. Ding, R.C. Yang, Q. Xiao and Y. Ju, *Synthesis*: Vol. 6 (2008), p. 0865

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