Arch Pharm Res Vol 27, No 8, 811-815, 2004

Archives of Pharmacal Research
http://apr.psk.or.kr

Solid Phase Synthesis of 3-(4-Hydroxyphenyl)coumarin: Preliminary Experiments for Combinatorial Synthesis of Substituted 3-Phenylcoumarin Derivatives

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(Received June 23, 2004)

Coumarin and its derivatives occur widely in nature. Many attempts were made for synthesis of various coumarin derivatives because of their interesting biological activities. In this study, solid phase synthetic approach of 3-(4-hydroxyphenyl)coumarin was achieved for combinatorial synthesis of substituted 3-phenylcoumarin analogues. Starting from 4-hydroxyphenylacetic acid methyl ester, release of 3-(4-hydroxypnehyl)coumarin from polymer support was accomplished.

Key words: Polymer-supported, Solid phase, Coumarin, 3-Phenylcoumarin, 3-Phenylchromenone, Arylcoumarin, 3-(4-Hydroxyphenyl)coumarin

INTRODUCTION

Coumarin derivatives occur widely in nature, particularly in plants; most of them show a variety of biological activities (Frukawa, 2000; Maier, 2000; Delgado, 2000; Chen, 2000; Khalmuradov, 1999; Jegadeesan, 1999; Gafner, 1999; Apers, 1998; Bal-Tembe, 1996; Abad, 1996; Chung, 1996; Celia do Nascimento, 1994; Botta, 1991; Fukuda, 1991). Many synthetic methods for coumarins have been reported (Fylaktakidou, 1998; Fall, 2000; Naser-Hijazi, 1994).

Here we show simple synthetic method of 3-phenylcoumarin on solid phase by four steps from 3-hydroxyphenylacetic acid methyl ester. This work will be a basis for convenient combinatorial synthesis for 3-phenylcoumarins having various substituents. In addition, 3-phenylcoumarin derivatives can be modified to isoflavenes (Gaudry, 1998) and isoflavans (Bradshaw, 1983) which would show a broad spectrum of biological activities (Fig. 1).

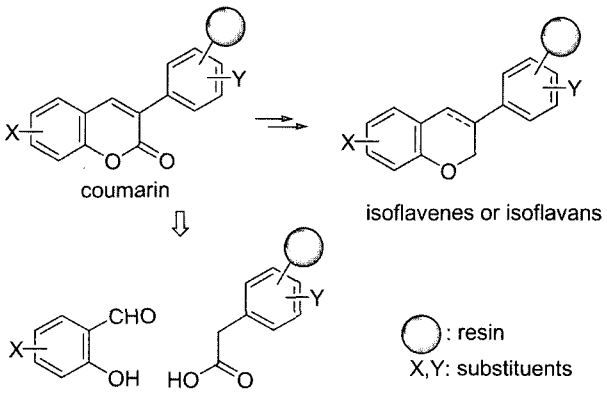

Fig. 1. Retrosynthetic analysis and possible modification of coumarins

MATERIALS AND METHODS

Chemicals

Mass spectra were taken with a Quattro LC, Micromass UK Ltd., UK. ^{1}H-NMR spectra were taken at a Bruker ARX 400 spectrometer using TMS as an internal standard. Silica gel 60 (Art 7734, 70-230 mesh) was used for open column chromatography. TLC was performed on silica gel 60 F_{254} (Merck DGaA, Germany). All necessary chemicals were purchased from Sigma-Aldrich Corp. (USA) if it is not specified. Quantitative analysis of Merrifield resin was 2 meq/Cl/g.

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Chemistry

4-Hydroxyphenylacetic acid (2)

A mixture of 4-methoxyphenylacetic acid (5 g, 30.1 mmol) and pyridine hydrochloride (20 g, 173 mmol) was heated at 220 °C for 2 h. It was then cooled and diluted with water (150 mL). The solution was cooled on ice bath and then concentrated. 6N HCl (50 mL) was added by dropping funnel. The aqueous acidic solution was extracted by ethyl acetate (100 mL×2), and then the organic layer was washed with water (100 mL×2), dried over anhydrous sodium sulfate, concentrated *in vacuo*. The residue was under titration with a mixed solution of hexane and ethyl acetate (2 : 1) and the precipitate was filtrated to give 4-hydroxyphenylacetic acid **2** (3.5 g, 76%) as a white solid. ^{1}H-NMR ($CDCl_3$ + one drop DMSO-d_6) δ 8.11 (bs, 1H), 7.10 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 8.1 Hz, 2H) 3.5 (s, 2H).

4-Hydroxyphenylacetic acid, methyl ester (3)

To a stirred solution of 4-hydroxyphenylacetic acid (**2**) (3.2 g, 21.03 mmol) in methanol (30 mL) was added one drop of concentrated sulfuric acid at room temperature. The reaction mixture was refluxed for 2 h, cooled to room temperature, concentrated *in vacuo*. The residue was dissolved into ethyl acetate (100 mL), washed with distilled water (50 mL×2). The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* to give methyl ester **3** (3.5 g, 100%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.08 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.3 Hz, 2H), 6.43 (bs, 1H), 3.69 (s, 3H), 3.55 (s, 2H).

4-Benzyloxyphenylacetic acid (5)

To a mixture of 4-hydroxyphenyl acetic acid methyl ester (**3**) (1.0 g, 6.01 mmol), tetrabutylammonium iodide (111 mg, 0.300 mmol), potassium iodide (3.32 g, 24.0 mmol) in dimethyl formamide (20 mL) at room temperature was neatly added benzyl chloride (1.4 mL, 12.2 mmol). After stirring for 6 h at 70 °C, the reaction mixture was cooled to room temperature and partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was separated and washed with water (50 mL×5), dried over anhydrous sodium sulfate, concentrated *in vacuo* to give crude (4-benzyloxyphenyl)acetic acid methyl ester (**4**) (2.5 g) which was used in the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ 7.27-7.45 (m, 5H), 7.22 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 3.71 (s, 3H), 3.59 (s, 2H).

The methyl ester **4** (crude 2.5 g) was dissolved in methanol (30 mL) and water (5 mL), and solid sodium hydroxide (720 mg, 18.0 mmol). After stirring for 4 h at room temperature, the reaction mixture was concentrated *in vacuo* to remove methanol. The aqueous mixture was diluted with water (5 mL), acidified by concentrated hydrochloric acid. The white precipitate was collected by filtration and washing with methanol (5 mL) to give 4-benzyloxyphenylacetic acid **5** (1.26 g, 79% two steps yield). ^{1}H-NMR ($CDCl_3$) δ 7.28-7.49 (m, 5H), 7.21 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 5.05 (s, 2H), 3.60 (s, 2H).

3-(4-Benzyloxyphenyl)coumarin (6)

A mixture of 4-benzyloxyphenylacetic acid (**5**) (500 mg, 2.06 mmol), salicylaldehyde (241 μL, 2.27 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (473 mg, 2.47 mmol), 4-dimethylaminopyridine (61 mg, 0.50 mmol) in DMF was stirred at room temperature for 6 h. The reaction was monitored with TLC analysis and a complete consumption of the starting materials was confirmed. The reaction mixture was partitioned between ethyl acetate (150 mL) and water (100 mL). The organic layer was washed with water (100 mL×3). Although washing with water several times could cause loss of product, it was done for high purity of product. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo*. The residue was used in the next reaction without further purification. (It was found out that the esterification was accompanied by ring closure, which gave a mixture of phenyl ester **5** and coumarin **6**, ring closure product).

The mixture was dissolved in methylene chloride (30 mL), followed by addition of 20% aqueous potassium carbonate (30 mL) and tetrabutylammonium hydrogen sulfate (100 mg, 0.295 mmol). The reaction mixture was stirred at room temperature for 4 h. Volatile methylene chloride was removed *in vacuo*. This operation gave white precipitate which was collected by filtration. The filter cake was washed with 20% aqueous potassium carbonate solution (80 mL) to removed hydrolyzed salicylaldehyde. The solid was sequentially washed with water (100 mL) and dried to give 3-(4-benzyloxyphenyl)coumarin (**6**) (310 mg, 46%). ^{1}H-NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.28-7.63 (m, 9H), 7.06 (d, J = 9.0 Hz, 2H), 5.13 (s, 2H).

Solid phase synthesis of 3-(4-hydroxyphenyl) coumarin (10)

Merrifield resin (1.0 g, 2 mmol based on Cl) was suspended in anhydrous dimethylformamide (10 mL), treated with 4-hydroxyphenylacetic acid methyl ester (**2**) (997 mg, 6 mmol) and tetrabutylammonium iodide (120 mg, 0.321 mmol) and potassium iodide (100 mg, 0.602 mmol) and potassium carbonate (3.4 g, 25.5 mmol) at 70-80 °C for 17 h. The reaction mixture was cooled to room temperature and water (10 mL) was added. After stirring for 10 min, the resin was filtrated, washed with water (100 mL), dimethyl formamide (20 mL), methanol (50 mL),

dried to give **7** (1.29 g, 87% based on measuring weight).

The methyl ester group of the alkylated resin **7** was hydrolyzed by water (10 mL), methanol (10 mL) and sodium hydroxide (1.5 g, 37.5 mmol) at 55 °C for 16 h. The mixture was cooled to room temperature, acidified by concentrated hydrochloric acid until pH was *ca.* 2, filtered, and the filter cake was washed with water (50 mL), methanol (100 mL), water (50 mL), methanol (50 mL) to give **8** (1.26 g, ~100% crude yield). This procedure was repeated to get a large quantity of acid resin **8**.

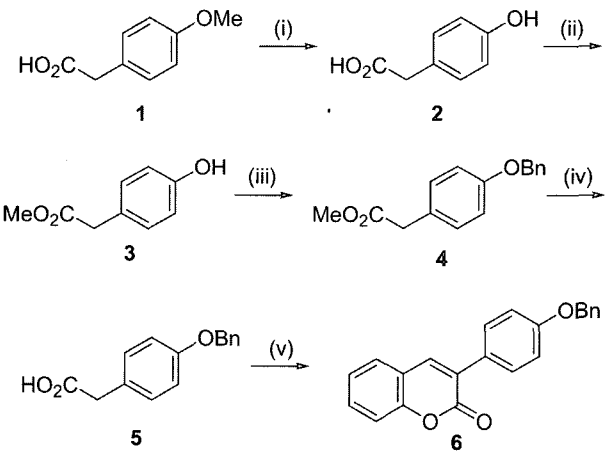
Phenyl acetic acid resin **8** (6 g) was suspended in dimethyl formamide (100 mL), treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (12 g, 62.5 mmol), salicylaldehyde (10 g, 81.9 mmol). The mixture was stirred at 55-60°C for 4 days. The progress of the reaction reached ring closure to give resin-linked 3-phenylcoumarin (**9**) (6.72 g, 88% based on measuring weight) in one pot.

The cyclized resin **9** (100 mg) was suspended in methylene chloride (2 mL), treated with sodium iodide (100 mg, 0.667 mmol) and trimethylsilyl chloride (1 mL). After stirring overnight at room temperature, the resin was filtered off and washed with methylene chloride (20 mL). The filtrate was washed with water (3 mL×2), 10% aqueous sodium thiosulfate (5 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* to give 3-(4-hydroxyphenyl)coumarin (**10**) (18 mg, 63% from Merrifield resin and 3-hydroxyphenylacetic acid methyl ester, the starting material). ^{1}H-NMR (DMSO-d_3) δ 9.73 (s, 1H, phenolic OH), 8.14 (s, 1H, vinylic H), 7.25 7.77 (m, 4H), 7.59 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.2 Hz); IR (KBr) 1710 (C=O), 1608 (C=C); *m/z* (EI) 238 (M^+), 210, 195.

RESULTS AND DISCUSSION

Before performing solid phase synthesis, model study was carried out for searching optimum reaction conditions which could be applied to solid phase chemistry. Previous synthetic methods for coumarin derivatives from carboxylic acid and salicylaldehyde had limitations in application to solid phase chemistry. Most of them were acetic anhydride-mediated conditions (Crawford, 1953) or harsh ones like high temperature in boiling diphenylether (boiling point 258 °C, Beauchamp, 2002). In order to avoid harsh reaction conditions we decided to search for relatively simple and mild synthetic condition.

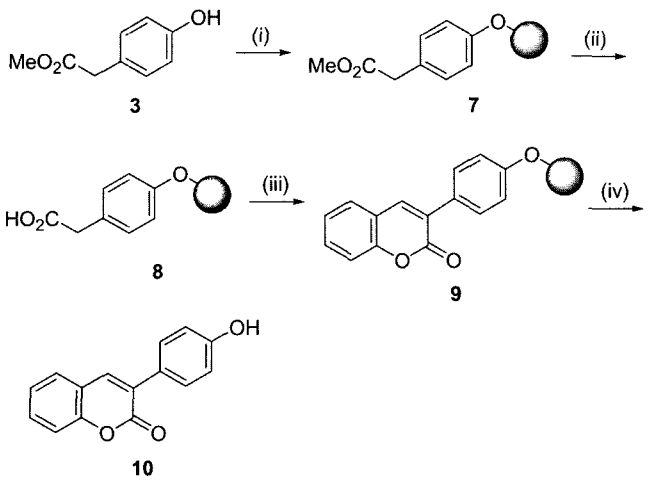
As shown in Scheme 1, synthesis of **6** began from 4-methoxyphenylacetic acid (**1**). Demethylation (Newman, 1976) on the methyl ether of 4-methoxyphenylaceticacid was successfully done by treatment of **1** with excess pyridine hydrochloride at 220 °C, which afforded 4-hydroxyphenylacetic acid (**2**) in 76% yield (Scheme 1).



Scheme 1. Synthesis of 3-benzyloxyphenylcoumarin (i) Pyr·HCl, 220 °C, 2 h, 76% (ii) MeOH, one drop of c-H_2SO_4, reflux, 2 h, 100% (iii) BnCl, K_2CO_3, KI, cat. TBAI, DMF, 70 °C, 6 h (iv) NaOH, MeOH/H_2O= 6:1, rt, 4 h, 79% two steps yield (v) salicylaldehyde, EDAC hydrochloride, DMAP, DMF, rt, 6 h, after work-up, 20% aqueous K_2CO_3, cat. $(Bu)_4N^+$ HSO_4^-, 46%.

Phenylacetic acid (**2**) was converted into phenylacetic acid methyl ester (**3**) by Fischer esterification (MeOH, cat. H_2SO_4). Benzylation (BnCl, K_2CO_3, KI, TBAI) on phenolic OH of **3** and successive treatment of the benzyl methyl ester **4** with NaOH in a mixed solution of MeOH/H_2O (6/1) at room temperature furnished benzyloxyphenylacetic acid (**5**) in 79% three steps yield. Coupling of **5** with salicylaldehyde was accomplished by treatment with EDAC, DMAP in DMF. However it was so hard to control the reaction condition to stop the progress to further intramolecular cyclization. As a result, it gave a mixture of ester and a cyclized compound **6**. When the mixture was treated with 20% aqueous K_2CO_3 in the presence of tetrabutylammonium hydrogen sulfate, a desired 4-hydroxyphenylcoumarin **6** was obtained in 46% two steps yield.

With successful result from model study, reaction conditions above were applied to solid phase synthesis of 4-hydroxyphenylcoumarin on Merrifield resin (Scheme 2). Reaction progress on solid phase synthesis was monitored by IR (KBr). *O*-Alkylation on Merrifield resin was accomplished by treatment of 4-hydroxyphenylacetic acid methyl ester **3** with the same condition as model study (**3** → **4**) except temperature and reaction time (70-80 °C, 17 h). Methyl ester group of **7** was hydrolyzed by excess sodium hydroxide to afford resin-linked phenylacetic acid **8**. In the last step on solid phase, formation of ester and ring cyclization reaction was achieved in one pot. Therefore treatment of **8** with salicylaldehyde, EDAC, DMAP in DMF at 55-60 °C for 4 days gave a desired coumarin **9**. Benzyl bond of **9** was cleaved by TMSI generated *in situ* (TMSCl, NaI, DCM) at room temperature to furnish 3-(4-



Scheme 2. solid phase synthesis of 3-hydroxyphenylcoumarin (i) merrifield resin, K_2CO_3, KI, cat. TBAI, DMF, 70-80 °C, 17 h (ii) NaOH, MeOH/H_2O=1/1, 50 °C, 16 h (iii) salicylaldehyde, EDAC hydrochloride, DMAP, DMF, 55-60 °C, 4 d (iv) TMSCl, NaI, CH_2Cl_2, rt, overnight. 46% from Merrifield resin as starting material.

hydroxyphenyl)coumarin (**10**) in 46% yield. For structural confirmation of **10**, it was converted to **6** by treatment with BnCl, K_2CO_3, KI and TBAI in DMF. The spectral data was identical to **6** synthesized in Scheme 1.

Based on the successful synthesis of 3-arylcoumarin on solid phase, synthetic work of various substituted 3-arylcoumarin analogues and conversion of a coumarin to the corresponding isoflavan and isofavene on solid phase are currently under investigation.

ACKNOWLEDGEMENT

This research was supported by Wonkwang University in 2004.

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