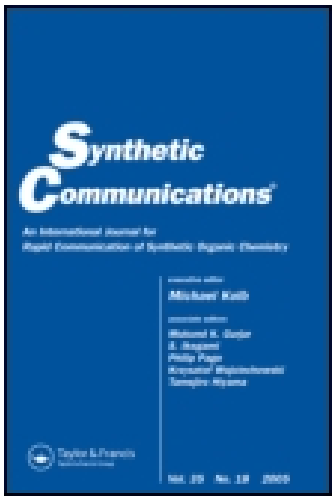

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J. Kadokawa [a c], T. Nishikura [a], R. Muraoka [a], H. Tagaya [a] & N. Fukuoka [b]

[a] Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, Yonezawa, Japan

[b] Chemipro Kasei Kaisha Ltd., Chuo-ku, Kobe, Japan

[c] Department of Materials Chemistry, Graduate School of Engineering, Tohoku University, Aoba 07, Aoba-ku, Sendai 980-8579, Japan Fax: E-mail:

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Synthesis of Kojic Acid Derivatives Containing Phenolic Hydroxy Groups

J. Kadokawa,[1,*] T. Nishikura,[1] R. Muraoka,[1] H. Tagaya,[1] and N. Fukuoka[2]

[1]Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, Yonezawa, Japan
[2]Chemipro Kasei Kaisha Ltd., Chuo-ku, Kobe, Japan

ABSTRACT

Two kojic acid derivatives (**2a** and **2b**) containing phenolic hydroxy groups were synthesized. The preparation was carried out by the reaction of a kojic acid derivative (**3**) having a chloromethyl group with phenol derivatives (**4** and **7**), followed by the subsequent deprotection steps. The first reaction proceeded smoothly in the presence of potassium carbonate in DMF at room temperature. Then, the appropriate deprotection reactions gave the desired compounds **2a** and **2b**. The structures of **2a** and **2b** were confirmed by the ^{1}H NMR spectra.

*Correspondence: J. Kadokawa, Department of Materials Chemistry, Graduate School of Engineering, Tohoku University, Aoba 07, Aoba-ku, Sendai 980-8579, Japan; Fax: 481-22-2188231; E-mail: kadokawa@poly.che.tohoku.ac.jp.

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Key Words: Kojic acid; Phenolic hydroxy group; Tylosinase inhibitor; Deprotection.

INTRODUCTION

Kojic acid (**l**), isolated from fermentative products of *Aspergillus* species, inhibits tyrosinase due to chelation of its copper, which is indispensable for tyrosinase activity.[1] The acid, therefore, had been used as a whitening agent for cosmetics and an antibrowning agent for food because of its inhibitory effects on melanin synthesis, which was resulted by tyrosinase activity.[2] On the other hand, the degree of inhibition by **1** is not sufficient enough for use in the above mentioned applications. On the other hand, it is well known that some natural compounds containing phenolic hydroxy groups, such as vitamin E and arbutin also act as tyrosinase inhibitors.[3,4]

Based on these viewpoints, we designed and synthesized new kojic acid derivatives containing phenolic hydroxy groups, which can be expected to have stronger inhibitory potency against tyrosinase than that of **1**. Two compounds have been synthesized here, which are 3-hydroxy-6-[(4-hydroxyphenoxy)methyl]-4*H*-pyran-4-one (**2a**) and 3-hydroxy-6-[(3,4-dihydroxyphenoxy)methyl]-4*H*-pyran-4-one (**2b**) having one and two phenolic hydroxy groups, respectively (Fig. 1).

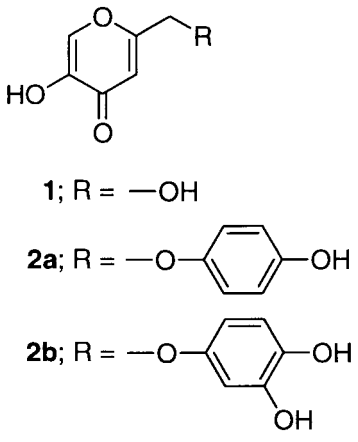


Figure 1. Structures of kojic acid derivatives.

EXPERIMENTAL

General

Compounds **3**, **4**, and **7** were prepared according to the literature.[5–7] Solvents were purified according to the usual manners. Other reagents were used without further purification. ^{1}H NMR spectra were recorded on a Varian Mercury 200 spectrometer.

Synthesis of 2a

Under argon, a solution of **3** (1.49 g, 6.00 mmol), **4** (2.00 g, 10.0 mmol), and K_2CO_3 (1.38 g, 10.0 mmol) in DMF (15.0 mL) were stirred at room temperature for 9 h. After the reaction mixture was concentrated by evaporation, the residue was poured into water, extracted with chloroform, washed successively with 1 mol/L H_2SO_4 aqueous, $NaHCO_3$ aqueous, and water. The chloroform layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by recrystallization from toluene to give **5** (1.44 g, 3.49 mmol) in 58.2% yield. Then, **5** (1.36 g, 3.30 mmol) was dissolved in **THF** (27.2 mL) and the solution was stirred in the presence of 10% Pd-C (0.136 g) at room temperature for 1.5 h under hydrogen atmosphere. After the filtration and evaporation of the reaction mixture, the crude product of **6** (0.924 g, 2.88 mmol) was obtained in 87.3% yield. A solution of **6** (0.841 g, 2.62 mmol) in methanol (20.2 mL) was stirred in the presence of 10% Pd-C (0.126 g) at room temperature for 1.5 h under hydrogen atmosphere. After the filtration and evaporation of the reaction mixture, the residue was washed with hot ethanol to give **2a** (0.150 g, 0.651 mmol) in 24.8% yield. ^{1}H NMR (DMSO-d_6) δ 4.87 (s, CH_2-O, 2H), 6.48 (s, CH-C=O, 1H), 6.68, 6.84 (2d, $J = 8.8$ Hz, C_6H_4, 4H), 8.10 (s, O-CH=, 1H), 9.04, 9.20 (2s, OH, 2H).

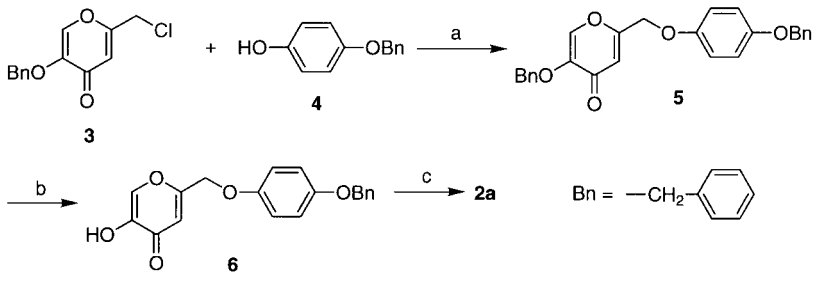
Synthesis of 2b

Under argon, a solution of **3** (0.33 g, 1.31 mmol), **7** (0.27 g, 1.31 mmol), and K_2CO_3 (0.18 g, 1.31 mmol) in DMF (2.0 mL) were stirred at room temperature for 4 h. After the reaction mixture was concentrated by evaporation, the residue was poured into water and extracted with chloroform. The chloroform layer was dried over Na_2SO_4, filtered, and evaporated to give a crude **8** (0.46 g, 1.09 mml) in 83.5% yield. Then,

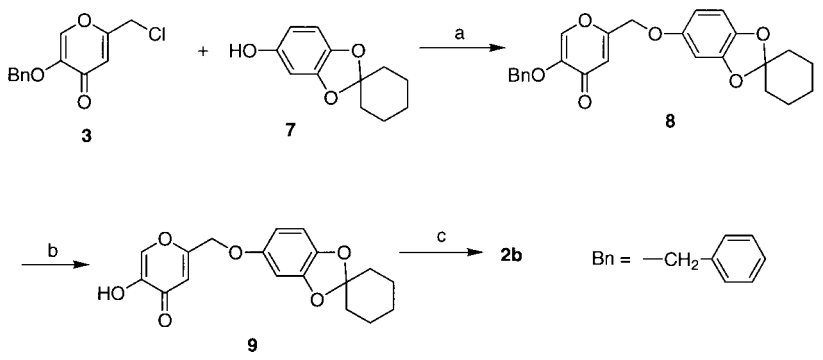
8 (0.20 g, 0.47 mmol) was dissolved in methanol (4.0 mL) and the solution was stirred in the presence of 10% Pd-C (0.020 g) at 40°C for 1.5 h under hydrogen atmosphere. After the filtration and evaporation of the reaction mixture, the crude product of **9** (0.070 g, 0.21 mmol) was obtained in 44.5% yield. To a mixed solution of concentrated hydrochloric acid (1.32 mL) and ethanol (5.30 mL), which was preheated at 70°C for 1.5 h, **9** (0.070 g, 0.21 mmol) and water (13.2 mL) was added. The mixture was heated at 70°C for 1.5 h and cooled to room temperature. The reaction mixture was concentrated and dried under reduced pressure to give **2b** (0.030 g, 0.12 mmol) in 56.6% yield. ^{1}H NMR (DMSO-d_6) δ 4.83 (s, CH_2-O, 2H), 6.27–6.63 (m, aromatic protons, 3H), 6.46 (s, CH-C=O, 1H), 8.10 (s, O-CH=, 1H), 8.53, 8.97, 9.21 (3s, OH, 3H).

RESULTS AND DISCUSSION

As the synthetic design, the desired compounds **2a** and **2b** would be obtained by the reaction of a kojic acid derivative (3-benzyloxy-6-chloromethyl-4*H*-pyran-4-one, **3**) having the electrophilic moiety of a chloromethyl group with the corresponding phenol derivatives **4** and **7**, followed by several deprotection steps (Schs. 1 and 2). These three substrates were prepared according to the literature.[5–7] The nucleophilic substitution of **3** with **4** or **7** was carried out in the presence of potassium carbonate and the reaction was monitored by thin layer chromatography (TLC) on silica gel. Both the reactions from **4** and **7** took place smoothly at room temperature, which were completed for several hours. After the general work-up procedures, **5** was purified by recrystallization from toluene (58.2% yield from **3**), whereas **8** was obtained with enough purity for the subsequent reaction steps without further purification



Scheme 1. (a) K_2CO_3, DMF, r.t., 9 h; (b) H_2, Pd-C, THF, r.t., 1.5 h; (c) H_2, Pd-C,MeOH, r.t., 1.5 h.



Scheme 2. (a) K_2CO_3, DMF, r.t., 4 h; (b) H_2, Pd-C, MeOH, 40°C, 1.5 h; (c) HCl, EtOH/H_2O, 70°C, 1.5 h.

(83.5% yield from **3**). Then, we attempted to carry out the simultaneous deprotection of two benzyl groups in **5** by catalytic hydrogenation. The attempt, however, was not successful, probably due to the different natures of the two benzyl groups. Therefore, the deprotection of the benzyl groups was carried out by the step-by-step manner as shown in Sch. 1. First, the benzyl group of the kojic acid side was successfully cleaved in the presence of 10% Pd-C in THF solvent at room temperature under hydrogen atmosphere, giving rise to **6**. Then, cleavage of the other benzyl group took place by the similar hydrogenation in methanol solvent to give **2a**, which was purified by washing with hot ethanol. The structure of the product was confirmed by the ^{1}H NMR measurement. On the other hand, the deprotection of **8** was demonstrated as follows. First, the benzyl group was cleaved by the catalytic hydrogenation in methanol solvent to produce **9**. Then, an acidic hydrolysis of the cyclohexylidene acetal proceeded, leading to **2b**. The ^{1}H NMR data of the product fully supported the structure of **2b**.

In conclusion, we presently synthesized kojic acid derivatives (**2a** and **2b**) containing phenolic hydroxy groups. These novel compounds can be expected for the application as a whitening agent for cosmetics as well as an antibrowning agent for food. The evaluation of inhibitory effects of **2a** and **2b** on tyrosinase activity is now in progress.

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