Direct Conversion to 2-Phenyl-4-quinolones *via* a 4-Alkoxyflavylium Salt from a Naturally Occurring Flavanone

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A flavanone, in which a hydroxyl group at the 5-position was protected with a methyl group, converted to the corresponding 5-methoxy-2-phenyl-4-quinolone *via* flavylium salt under mild conditions. Flavanone-*O*-rhamnoglucoside, naringin, was also converted to 5-methoxy-2-phenyl-4-quinolon-7-*O*-rhamnoglucoside in the same way in an overall 25% yield.

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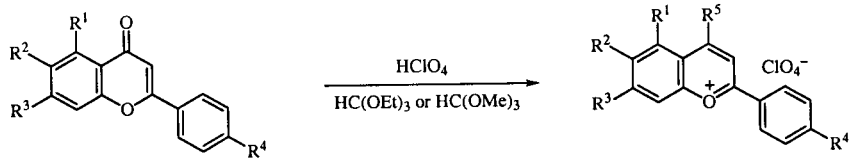
In a previous paper [1], we reported a convenient synthesis of a series of 2-phenyl-4-quinolone derivatives as antitumor agents [2], which were produced by the formation of 4-ethoxyflavylium perchlorates by the condensation of substituted acetophenones, benzaldehydes and ethyl orthoformate in the presence of perchloric acid with subsequent treatment with an aqueous ammonia solution. In the coarse of this synthetic study, it was found that this method also yielded a flavanone as an intermediate. Since it has been reported that a 4-ethoxyflavylium salt was also afforded from flavanone [3], we examined the application of this method to the direct conversion to 2-phenyl-4-quinolone from a naturally occurring flavanone. The conversion reaction of the 6-methylflavanone proceeded in the presence of 70% perchloric acid in ethyl orthoformate at 50° for 1 hour (or at room temperature for 1 day). 4-Ethoxy-6-methylflavylium perchlorate (**2a**) was obtained as brown crystals in 41% yield. Compound **2a** was converted to the corresponding 6-methyl-2-phenyl-4-quinolone (**3a**) by stirring in a 25% aqueous ammonia solution at room temperature for 3 hours. Although we examined the conversion reaction of the naturally occurring flavanones, naringenin (4',5,7-trihydroxyflavanone) and naringin (naringenin-7-*O*-rhamnoglucoside) in ethyl or methyl orthoformate in the presence of 70% perchloric acid, neither gave the corresponding 4-ethoxyflavylium perchlorate (entries 2 and 3). Because the reason of this failure was assumed to be due to 5-hydroxyl group, 5-hydroxyflavanone was synthesized and employed in the conversion reaction. The directed conversion of 5-hydroxyflavanone was unsuccessful. However, when its 5-hydroxyl group was protected with a methyl group, the conversion reaction proceeded to give 4,5-dimethoxyflavylium perchlorate in 32% yield (Table 1, entry 4), which was subsequently converted to 5-dimethoxy-2-phenyl-4-quinolone (**3d**) in 25% aqueous ammonia solution at room temperature in 79% yield (Table 2, entry 2). When using ethyl orthoformate, the yield

Table 1
Conversion of Flavanones to Flavylium Perchlorates

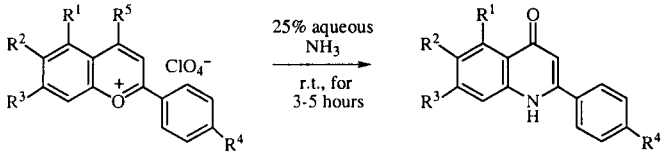


1a-j **2a,d,e,f,j**

Entry	flavanone	R^1	R^2	R^3	R^4	R^5	Temperature (°C)	Time (hours)	Product	Yield (%)
1	**1a**	H	Me	H	H	OEt	50 (r.t.)	1 (24)	**2a**	41
2	**b**	OH	H	H	H	OEt	50	10	-	0
3	**c**	OH	H	O-Glc-Rha	OH	OEt	50	10	-	0
4	**d**	OMe	H	H	H	OMe (OEt)	50	10	**d**	32 (26)
5	**e**	OMe	H	OMe	OMe	OMe	60	7	**e**	74
6	**f**	OMe	H	OMe	OH	OMe	50	10	**f**	40
7	**g**	OMe	H	OMe	OAc	OMe	60	10	-	0
8	**h**	OAc	H	OAc	OAc	OMe	60	10	-	0
9	**i**	OAc	H	O-Glc(OAc)$_3$-Rha(OAc)$_3$	OAc	OMe	60	10	-	0
10	**j**	OAc	H	O-Glc-Rha	OH	OMe	60-70	10	**j**	60

of the corresponding 4-ethoxyflavylium perchlorate was lower (26%), thus methyl orthoformate was used in later experiments. When a natural naringenin was reacted after protecting all of its 4',5, and 8-hydroxyl group as the methyl ethers, the conversion reaction proceeded smoothly to afford

Table 2
Conversion Reaction of Flavylium Perchlorates to 2-Phenyl-4-quinolones



2a,d,e,f,j **3a,d,e,f,j**

Entry	Product	Yield (%)
1	**3a**	78
2	**d**	79
3	**e**	48
4	**f**	70
5	**i**	42

the corresponding 4-ethoxyflavylium perchlorate (**2e**) in 74% yield (Table 1, entry 5), which was subsequently converted to the corresponding 5,7-dimethoxy-2-(4'-methoxyphenyl)-4-quinolone (**3e**) in 48% yield (Table 2, entry 3). 5,8-Dimethoxynaringenin was also converted to the corresponding 5,7-dimethoxy-2(4'-hydroxyphenyl)-4-quinolone (**3f**) in the same manner (Table 1, entry 6 and Table 2, entry 4). When each of the hydroxyl groups were protected as an acetate, the reaction did not proceed (entries 7, 8, and 9). It was established that protection of the hydroxy group at the 5-position as an ether was required for the conversion to the 4-ethoxyflavylium salt from the flavanone. An exception may be the hydrogen bonding between the 5-hydroxy group and the carbonyl oxygen in the flavanone for the formation of the 4-ethoxyflavynium salt. Finally, the conversion reaction of the *O*-glycosylflavanone, naringin was allowed to react at 60~70° for 10 hours after protection of its 5-hydroxy group to afford the corresponding 4-ethoxyflavylium salt without cleavage of the glycosidic linkage in 60% yield. Its subsequent treatment in a 25% aqueous ammonia solution gave 5-methoxy-2-(4'-hydroxy)phenyl-4-quinolon-7-*O*-rhamnoglucoside in 42% yield (see Table 1, entry 10 and Table 2, entry 5). It was shown that 2-phenyl-4-quinolone could be converted from the naturally occurring glycosylflavanone by this new two-step synthetic method. Thus this mild and direct conversion method may be one of the more convenient, efficient and versatile synthetic methods for substituted 2-phenyl-4-quinolone derivatives with further application to natural products. The evaluation of these products as antitumor agents is now in progress.

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EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Mass spectra (ms) data were obtained by Electron Ionization (EI) or Fast Atom Bombardment (FAB) method using 3-nitrobenzyl alcohol as the matrix on a JEOL HX 100 mass spectrometer. Infrared (ir) spectra were recorded on a Horiba FT-200 IR spectrometer as potassium bromide pellets. Elemental analyses were performed on a Perkin-Elmer PE 2400 II. The ^{1}H nmr spectra were measured at 60 MHz on a HITACHI H-60 or at 270 MHz on a JOEL 270 or at 200 MHz on a Varian 200 spectrometer, while the ^{13}C nmr spectra were obtained at 67.8 MHz on a JOEL 270 or at 50 MHz on a Varian 200 spectrometer. They were recorded in deuteriochloroform or deuteriodimethyl sulfoxide and in deuteriotrifluoroacetic acid for flavylium salts. Chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethyl silane. Flash chromatography was performed on silica gel (230-400 mesh, Fuji silysia Co. Ltd., BW-300) using ethyl acetate or a mixture of chloroform and methanol as eluents.

General Procedure.

6-Methyl and 5-hydroxyflavanones were synthesized by the aldol condensation of 5-methylacetophenone or phloroacetophenone, and benzaldehyde and subsequent thermal ring closure using sulfuric acid, respectively.

4-Ethoxyflavylium Salt.

To a stirred solution of flavanone (100 mg, 0.32 mmole) in methyl orthoformate (5 ml), 70% perchloric acid (70 mg, 0.48 mmole) was added slowly at room temperature and the mixture was stirred at 50-60° for *ca.* 2 hours. The reaction mixture was allowed to stand for 1 day at room temperature and then resulting precipitate was filtered to give to the 4-ethoxyflavylium perchlorate (59 mg, 43%) as a brown precipitate, which was employed in the next step without recrystalization.

4-Ethoxy-6-methylflavylium Perchlorate (**2a**).

This compound was obtained as described [1].

2-Phenyl-4-quinolone.

To a stirred 25% aqueous ammonia solution, the 4-ethoxyflavylium salt was added. The resulting suspension was vigorously stirred at room temperature for 3-5 hours until the disappearance of the material by alumina tlc monitoring (chloroform: methanol = 2:1), and then filtered and washed with water to give the product as orange crystals.

6-Methyl-2-phenyl-4-quinolone (**3a**).

This compound was obtained as described [1].

5-Methoxy-2-phenyl-4-quinolone (**3d**).

This compound was obtained as yellow needles (from ethyl acetate), mp 154-155° ms: (EI) (m/z) 251 (M^+, 100); ir ν 3330, 2944, 2844, 1650, 1606, 1587, 1477, 1238, 1093, 773, 694 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.98 (3H, s, OCH_3), 6.69 (1H, s, H-3), 6.75 (1H, dd, J = 0.8 and 8.3 Hz, H-6), 7.01 (1H, dd, J = 0.8 and 8.3 Hz, H-8), 7.41 (1H, t, J = 8.3 Hz, H-7), 7.44-7.86 (5H, m, ArH), 10.23 (1H, br. s, NH); ^{13}C nmr (deuteriopyridine): δ 56.0,

106.7, 108.7, 111.0, 125.7 (x2), 129.1 (x2), 130.4, 132.0, 132.6, 154.7, 155.1, 159.4, 160.1.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.24; H, 5.13; N, 5.32

5,7-Dimethoxy-2-(4'-hydroxy)phenyl-4-quinolone (**3e**).

This compound was obtained as a red powder; mp >300° ms: (FAB) (m/z) 298 $(M+H)^+$; ir ν 3421, 1637, 1581, 1455, 1360, 1157 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide at 80°): δ 3.88 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.45 (1H, s, H-3), 6.53 (1H, d, J = 2.2 Hz, H-6), 6.61 (2H, d, J = 9.0 Hz, H-3', 5'), 6.72 (1H, d, J = 2.2 Hz, H-8), 7.65 (2H, d, J = 9.0 Hz, H-2', 6').

5,7-Dimethoxy-2-(4'-methoxy)phenyl-4-quinolynolium perchlorate (**3f**).

This compound was obtained as a pale yellow-green prisms (from chloroform-methanol), mp 273° ms: (FAB) (m/z) 312 $(M+H)^+$; ir ν 3405, 3095, 2946, 2844, 1645, 1602, 1519, 1465, 1427, 1365, 1259, 1186, 1120 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 3.90 (3H, s, 7-OCH_3), 3.99 (3H, s, 5-OCH_3), 4.05 (3H, s, 4'-OCH_3), 6.81 (1H, d, J = 2.2 Hz, H-6), 7.13 (1H, s, H-3), 7.19 (1H, d, J = 2.2 Hz, H-8), 7.22 (2H, d, J = 8.9 Hz, H-3', 5'), 8.03 (2H, d, J = 8.9 Hz, H-2' and 6'), 9.55 (1H, br. s, NH), 10.00 (1H, br s, OH); ^{13}C nmr (deuteriodimethyl sulfoxide) : δ 55.6, 56.6, 57.1, 94.2, 97.0, 97.6, 98.6, 108.5, 114.8 (x2), 121.0, 128.4 (x2), 157.2, 158.8, 159.8, 161.9, 163.1, 166.4.

Anal. Calcd. for $C_{11}H_{18}ClNO_8$: C, 52.50; H, 4.41; N, 3.40. Found: C, 52.42; H, 4.41; N, 3.36.

5-Methoxy-8-*O*-rhamunoglucosyl-2-(4'-hydroxy)phenyl-4-quinolone (**3j**).

This compound was obtained as a yellow prisms (from methanol), mp 244-245°; ms: (FAB) (m/z) 592 $(M+H)^+$; ir: ν 2916, 1637, 1602, 1585, 1515, 1486, 1348, 1168, 1132, 1074, 1047, 829 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide + deuterium oxide): δ 1.23 (3H, d, J = 6.0 Hz, H-2', 4'), 3.18-5.27 (12H, m, sugar moiety), 3.96 (3H, s, OCH_3), 6.53 (2H, d, J = 8.9 Hz, H-3', 6'), 6.59 (1H, d, J = 2.0 Hz, H-6), 6.62 (1H, s, H-3), 6.88 (1H, d, J = 2.0 Hz, H-8), 7.65 (2H, d, J = 8.9 Hz, H-2', 4').

Anal. Calcd. for $C_{28}H_{33}NO_3 \cdot 2H_2O$: C, 53.57; H, 5.94; N, 2.23. Found: C, 53.76; H, 6.17; N, 2.12.

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