Novel Chlorination of 4',5,7-Trihydroxyflavanone with Cupric Chloride-Oxygen

Yasuomi Takizawa and Tatsuo Mitsuhashi

Department of Chemistry, Tokyo Gakugei University, 4-1-1, Nukuikita-machi, Koganei-shi, Tokyo 184, Japan,

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Novel chlorination of 4',5,7-trihydroxyflavanone with copper(II) chloride and oxygen is described. 6,8-Dichloro-4',5,7-trihydroxyflavanone (**2**) and 6,8-dichloro-4,4',5,7-tetraacetoxyflav-3-ene (**3**) were newly synthesized.

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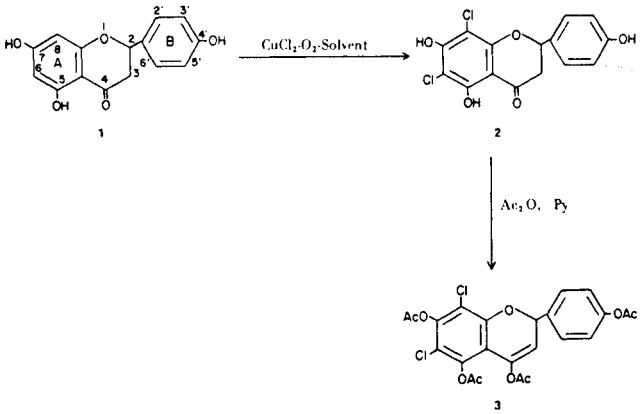
Sir:

In the course of the study of oxidative coupling of naringenin (4',5,7-trihydroxyflavanone), we found chlorination of naringenin in high yield by use of copper(II) chloride and oxygen. The liquid-phase chlorination of olefins and acetylenes with copper(II) chloride-lithium chloride in acetonitrile at 82° is also known (1). Previously, chlorination of flavone with zinc chloride-hydrochloric acid was reported by us (2). The reaction conditions of these methods are not mild in the point of using high temperature or strong acid. However, this method is very useful for selective chlorination of the A-ring of hydroxyflavonoids without chlorination of the B-ring by using mild condition (40°) and simple reaction system (cupric chloride, oxygen, alcohol) comparing with other methods. We wish to report the efficient synthesis of 6,8-dichloro-4',5,7-trihydroxyflavanone (**2**) and 6,8-dichloro-4,4',5,7-tetraacetoxyflav-3-ene (**3**).

$$\mathbf{1} \xrightarrow{CuCl_2\text{-}O_2\text{-Solvent}} \mathbf{2} \xrightarrow{Ac_2O,\ Py} \mathbf{3}$$

Naringenin (1.0 mmole) and copper(II) chloride (2.0 mmoles) were added in various solvents (50 ml.). The reaction was carried out by bubbling oxygen through a solution with stirring at 40° for 12 hours. The reaction mixture was examined by tlc (benzene-ethyl acetate; 2:1) and the product was detected by iodine vapor and spraying with concentrated sulfuric acid. The product was isolated by silica gel chromatography. This product was positive to a Beilstein test (3) and determined as 6,8-dichloro-4',5,7-trihydroxyflavanone (**2**) by the following physical and spectral data: m.p. 227.0-228.0°; ir (potassium bromide): 3550, 3300, 1640, 1610, 1510, 1450, 870, and 750 cm^{-1}; nmr (δ, deuterioacetone): 3.00-3.40 (3H, methine and methylene), 6.85 (2H, d, 3'-H and 5'-H), 7.39 (2H, d, 2'-H and 6'-H), 12.58 (1H, s, 5-H, exchangeable with deuterium oxide); ms: m/e 340 (M^+ for $C_{15}H_{10}O_5Cl_2$), m/e 220 (M^+ - C_8H_8O), m/e 120 ($C_8H_8O^+$).



1 2 3

The nmr and ms spectra revealed that the B-ring of the flavanone was not substituted by chlorine. Compound **2** was acetylated by acetic anhydride and pyridine. The acetylated compound was found to be 6,8-dichloro-4,4',5,7-tetraacetoxyflav-3-ene (**3**) by the following physical and spectral data: m.p. 185.0-186.0°; ir (potassium bromide): 1785, 1700, 1590, and 1600 cm^{-1}; nmr (δ, deuteriochloroform): 2.30 and 2.50 (12H, 4 x $OCOCH_3$), 3.20 (1H, d, 2'-H), 6.80 (1H, d, 3-H), 6.84 (2H, d, 3'-H and 5'-H), 7.35 (2H, d, 2'-H and 6'-H); ms: m/e 508 (M^+ for $C_{23}H_{18}O_9Cl_2$), m/e 466 (M^+-C_2H_2O), m/e 424 (M^+ - 2 x C_2H_2O), m/e 382 (M^+ - 3 x C_2H_2O), m/e 340 (M^+ -4 x C_2H_2O). From an examination of the solvent effect in this reaction, ethyl alcohol and methyl alcohol are favored to produce compound **2**. (Table 1).

Table 1

Solvent Effect on the Chlorination of Naringenin

Solvents	Percent Yield of **2**
Methyl alcohol	75
Ethyl alcohol	80
Benzene	-
Ether	-
DMSO	-
DMF	-

REFERENCES AND NOTES

(1) S. Uemura, H. Okazaki, A. Onoe, and M. Okano, *J. Chem. Soc., Perkin Trans. I*, 676 (1977).

(2) Y. Omote, Y. Takizawa and N. Sugiyama, *J. Heterocyclic Chem.*, 8, 319 (1971), and references therein.

(3) F. Beilstein, *Ber.*, 5, 620 (1872).