A NEW SYNTHESIS OF DIHYDROISOCOUMARIN DERIVATIVES

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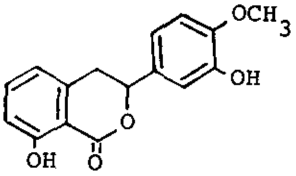
Dihydroisocoumarin derivatives including phyllodulcin analogues were synthesized in one step by the reaction of styrenes with o-carboxyphenylpalladium chloride.

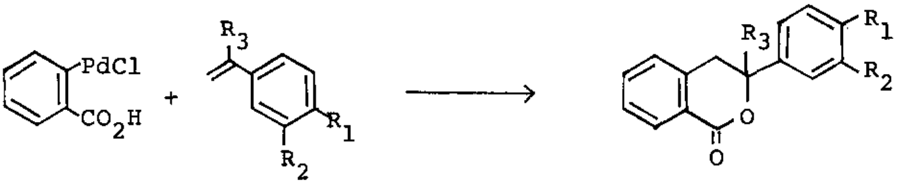
The naturally occurring 3,4-dihydroisocoumarin derivative, (+)-phyllodulcin (I), a sweet principle of Amacha (sweet tea) called attention to the relationship between the structures of some 3,4-dihydroisocoumarin and their biological activities.[1] Recently, the total synthesis of (±)-phyllodulcin have been reported.[2] On the other hand, we have found an addition reaction in which the aryl group of an arylpalladium chloride and the anion part of a protic solvent add to the double bond of olefins conjugated to benzene ring. By the use of o-hydroxyphenylpalladium chloride and 2H-chromene, this reaction was applied to the synthesis of (±)-pterocarpin.[3] The present paper reports further extension of the reaction, leading to one-step synthesis of 3,4-dihydroisocoumarin derivatives including



(I)

phyllodulcin analogues.

The reaction was carried out as follows. To a solution of lithium chloropalladite (2 mmol) in acetic acid (40 ml) or acetonitrile (20 ml), o-chloromercuriobenzoic acid (2.5 mmol) and the styrene (IIIa-IIIf, 3 mmol) were added, and the mixture was stirred for 2 to 3 hr at room temperature. The resulted palladium black was filtered off and the filtrate was diluted with an aqueous solution of sodium chloride. The mixture was extracted with benzene which was chromatographed on a silica gel column. Elution with benzene or benzene-ethyl acetate (10:1) gave the crystalline product (IVa-IVd).



(II)

(IIIa) $R_1,R_2=OCH_2O$, $R_3=H$

(IIIb) $R_1=R_2=OCH_3$, $R_3=H$

(IIIc) $R_1=OCH_3$, $R_2=OAc$, $R_3=H$

(IIId) $R_1=OAc$, $R_2=OCH_3$, $R_3=H$

(IIIe) $R_1=R_2=R_3=H$

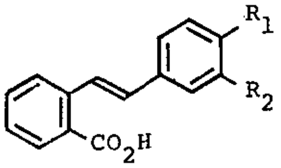
(IIIf) $R_1=R_2=H$, $R_3=CH_3$

(IVa) $R_1,R_2=OCH_2O$, $R_3=H$

(IVb) $R_1=R_2=OCH_3$, $R_3=H$

(IVc) $R_1=OCH_3$, $R_2=OAc$, $R_3=H$

(IVd) $R_1=R_2=H$, $R_3=CH_3$

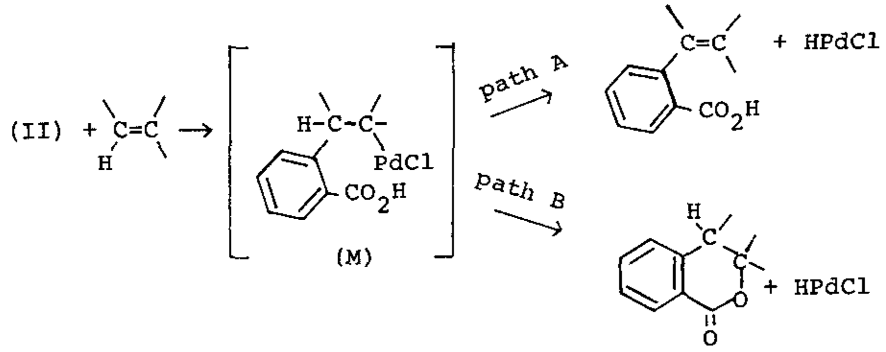


(Va) $R_1=OAc$, $R_2=OCH_3$

(Vb) $R_1=R_2=H$

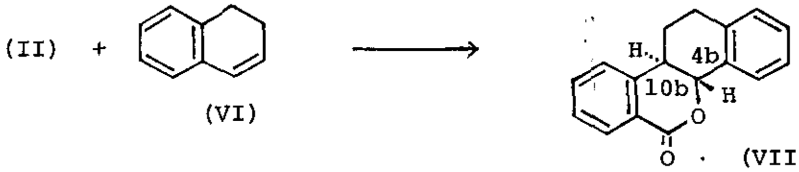
The reaction of (II) with 3,4-methylenedioxystyrene (IIIa), 3,4-dimethoxystyrene (IIIb), and 3-acetoxy-4-methoxystyrene (IIIc) afforded 3-(3,4-methylenedioxyphenyl)-3,4-dihydroisocoumarin (IVa; 58% yield in AcOH, 47% yield in CH_3CN),[4] 3-(3,4-dimethoxyphenyl)-3,4-dihydroisocoumarin (IVb; 29% yield in AcOH, 50% yield in CH_3CN),[5] and 3-(3-acetoxy-4-methoxyphenyl)-3,4-dihydroisocoumarin (IVc; 50% yield in AcOH, 60% yield in CH_3CN)[6] respectively. In addition to the physical properties of these compounds, the structure of IVc was further identified by the comparison to the acetylation product of 3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydroisocoumarin.[1]

However, the reaction of II with 4-acetoxy-3-methoxystyrene (IIId) or styrene (IIIe) gave o-(4-acetoxy-3-methoxystyryl)benzoic acid (Va) or o-carboxystilbene (Vb), respectively. The formation of the phenylated olefin Va or Vb is illustrated by the two step mechanism consisting of the addition of II to the double bond of IIId or IIIe, and the elimination of hydridopalladium chloride from the palladium complex (M) (path A). When the styrene moiety of the intermediate complex M has an electron-donating group, the carbonium ion which is produced by the S_N1 type cleavage of the carbon-palladium σbond[3] may be stabilized and react with the



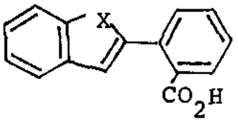
neighboring carboxyl group to give the dihydroisocoumarin compound (path B). This mechanism accounts for the high yield (83% in AcOH) in the formation of 3-methyl-3-phenyl-3,4-dihydroisocoumarin (IVd)[8] from II and IIIf.

Application of the reaction to 3,4-dihydronaphthalene (VI) produced tetracyclic 3,4-dihydroisocoumarin (VII; 45% yield in AcOH)[9] accompanying an acid (VIIIa; 28%). The stereochemistry of the B/C ring juncture in VII is determined to be trans.[10]



(VI)

(VII)



(VIIIa) X= $(CH_2)_2$

(VIIIb) X= CH_2

The reaction of indene with II gave o-(2-indenyl)benzoic acid (VIIIb) as the main product. As this isocoumarin synthesis can be carried out under mild conditions, it may be applicable to the synthesis of the naturally occurring oxygen compound containing a variety of functional group.

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4 mp 132-134°C. ir (KBr); 1705, 1610, 1262. nmr (δ, $CDCl_3$); 3.12 (2H, d, J 4Hz), 5.42(1H, dd, J 4Hz), 5.92(2H, s), 6.8-7.5(6H, m), 8.09(1H, m). All the products described in this report gave satisfactory elemental analysis.

5 mp 107-108°C. ir (KBr); 1705, 1602, 1280. nmr (δ, $CDCl_3$); 3.13(1H, d, J 4Hz), 3.86(3H, s), 3.87(3H, s), 5.47(1H, dd, J 4Hz), 6.8-7.6(6H, m), 8.78(1H, m).

6 mp 152-153.5°C. ir (KBr); 1760, 1705, 1605, 1275. nmr (δ, $CDCl_3$); 2.30(3H, s), 3.17(2H, d, J 4Hz), 3.83(3H, s), 5.45(1H, dd, J 4 Hz), 6.9-7.6(6H, m), 8.08(1H, m).

7 R. F. Heck, *J. Amer. Chem. Soc.*, 1968, **90**, 5518.

8 bp 145-149°C/2 Torr. ir (neat); 1720, 1290, 1115. nmr (δ, CCl_4); 1.69(3H, s), 3.40(2H, s), 7.06-7.44(8H, m), 7.90(1H, m).

9 mp 151°C. ir (KBr); 1705, 1285, 1085. nmr (δ, $CDCl_3$); 1.85(1H, m), 2.76(1H, m), 3.3-3.4(3H, m), 5.25(2H, d, J 12Hz), 7.42-7.80(7H, m), 8.15(1H, m).

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