A SIMPLE TWO STEP SYNTHESIS OF 6,8-DIHYDROXY-3-(3′,4′-DIHYDROXYPHENYLETHENYL)ISOCOUMARIN

Aamer Saeed* and Nasim H. Rama

Department of Chemistry
Quaid-i-Azam University
Islamabad 45320, Pakistan.

الخلاصة :

تم تحضير أيزوكومارين (٣) مخبرياً ، والذي استُخلص حديثاً من الأجزاء الارضية لنبات أكيلس تريبثالا . وأدّى التفاعل المباشر لحمض ٣،٥-داي ميثوكسيهوموفثلك (٤) مع كلوريد ٣،٤-داي ميثوكسيناميل (٥) إلى انتاج ٦ و ٨-داي ميثوكسي-(٣)- (٣′ و ٤′-داي ميثوكسيفينيل إيثينيل) أيزوكومارين (٦) . ومن ثم أُنتجت عملية نزع الميثيل من المركب (٦) باستخدام تراي بروميد البورون إلى انتاج أيزوكومارين (٣) بكمية معقولة .

ABSTRACT

The title isocoumarin (**3**) isolated recently from the underground parts of the plant *Achyls triphylla,* by other authors, has been synthesized. Direct reaction of 3,5-dimethoxyhomophthalic acid (**4**) with 3,4-dimethoxycinnamoyl chloride (**5**) afforded 6,8-dimethoxy-3-(3′,4′-dimethoxyphenylethenyl)isocoumarin (**6**). Complete demethylation of compound (**6**) was effected using boron tribromide in refluxing dichloromethane to give the title isocoumarin (**3**) in reasonable yield.

*To whom correspondence should be addressed.

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INTRODUCTION

In 1990, Mizuno and Yoshida *et al.* [1] carried out a chemical investigation of the plant *Achlys triphylla* (J. E. Sm) DC family berberidaceae, to determine its chemotaxonomic relationships with other members of the subtribe Epimedinae and to look for chemicals with medicinal properties. The isolation of three new phenolic compounds with a novel structure, from the underground parts of *A. triphylla,* was reported. The structures of the isolated compounds were established using IR, UV, PMR, CMR, and high resolution mass spectra. The isolated compounds were named as achlisocoumarin I, achlisocoumarin II, and achlisocoumarin III having the following structures:

Achlisocoumarin I (**1**):

7-geranyl-6,8-dihydroxy-3-(4′-hydroxyphenylethyl)isocoumarin.

Achlisocoumarin II (**2**, R^1 = geranyl, R^2 = H):

7-geranyl-6,8-dihydroxy-3-(4′-hydroxyphenylethenyl)isocoumarin.

Achlisocoumarin III (**3**, R^1 = H, R^2 = OH):

6,8-dihydroxy-3-(3′,4′-dihydroxyphenylethenyl)isocoumarin.

A simple synthesis of achlisocoumarin III (**3**) has been carried out.

SYNTHESIS OF 6,8-DIHYDROXY-3-(3′,4′-DIHYDROXYPHENYLETHENYL) ISOCOUMARIN (3)

A synthesis of the title isocoumarin was carried out by adopting the procedure of Nakajima *et al.* [2–4].

Commercially available 3,4-dimethoxycinnamic acid (predominantly *trans*) was converted to 3,4-dimethoxycinnamoyl chloride (**5**) at room temperature using oxalyl chloride in dry benzene. The use of thionyl chloride was avoided because of possible reaction with the double bond. A mixture of 3,5-dimethoxyhomophthalic acid (**4**) [5] and the acid chloride (**5**) (1:4 molar ratio) was heated at 200°C for 5 hours and then refluxed with methanol to convert the excess of acid chloride into the corresponding ester. The residue was purified by thick layer chromatography and precipitated to afford 6,8-dimethoxy-3-(3′,4′-dimethoxyphenylethenyl)isocoumarin (**6**) (56%) as a semisolid. IR showed strong absorptions at 1680 cm^{-1} for lactonic carbonyl and at 1602 and 1583 cm^{-1} for the aromatic system. PMR showed four three-proton singlets at δ 3.80–3.89 for the aromatic methoxy groups and the characteristic singlet for the highly conjugated H-4 at δ 6.60 ppm.

Complete demethylation of compound (**6**) was effected using an excess of boron tribromide in dichloromethane under reflux temperature to afford 6,8-dihydroxy-3-(3′,4′-dihydroxyphenylethenyl)isocoumarin (**3**) (54%) as a brownish amorphous powder. IR showed absorptions for phenolic OH at 3406 and 3244 cm^{-1} and lactonic carbonyl at 1626 cm^{-1}. The PMR data is recorded in Table 1 and compared with that reported in the literature [1].

Table 1 shows that, except for some experimental differences, there is close agreement between the PMR data for the reported isocoumarin and for the one presently synthesized.

EXPERIMENTAL

The IR spectra were recorded on a Hitachi spectrophotometer Model-270 as KBr discs or as neat liquids. PMR (360 MHz) spectra were recorded on a Bruker AM-300 as $CDCl_3$ solutions, using TMS as internal standard and the EIMS on a MAT-112-S machine.

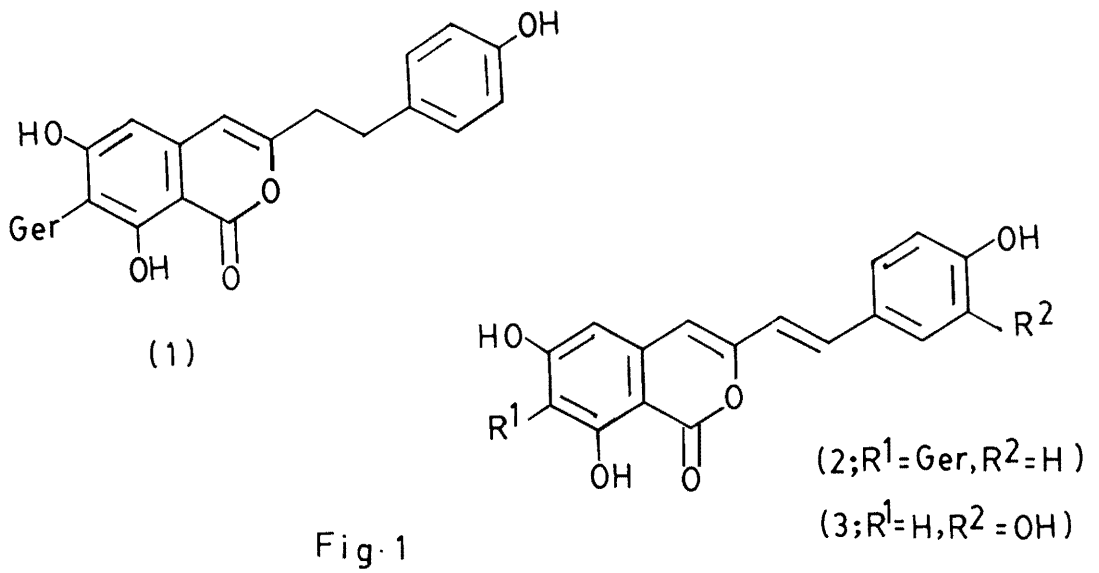
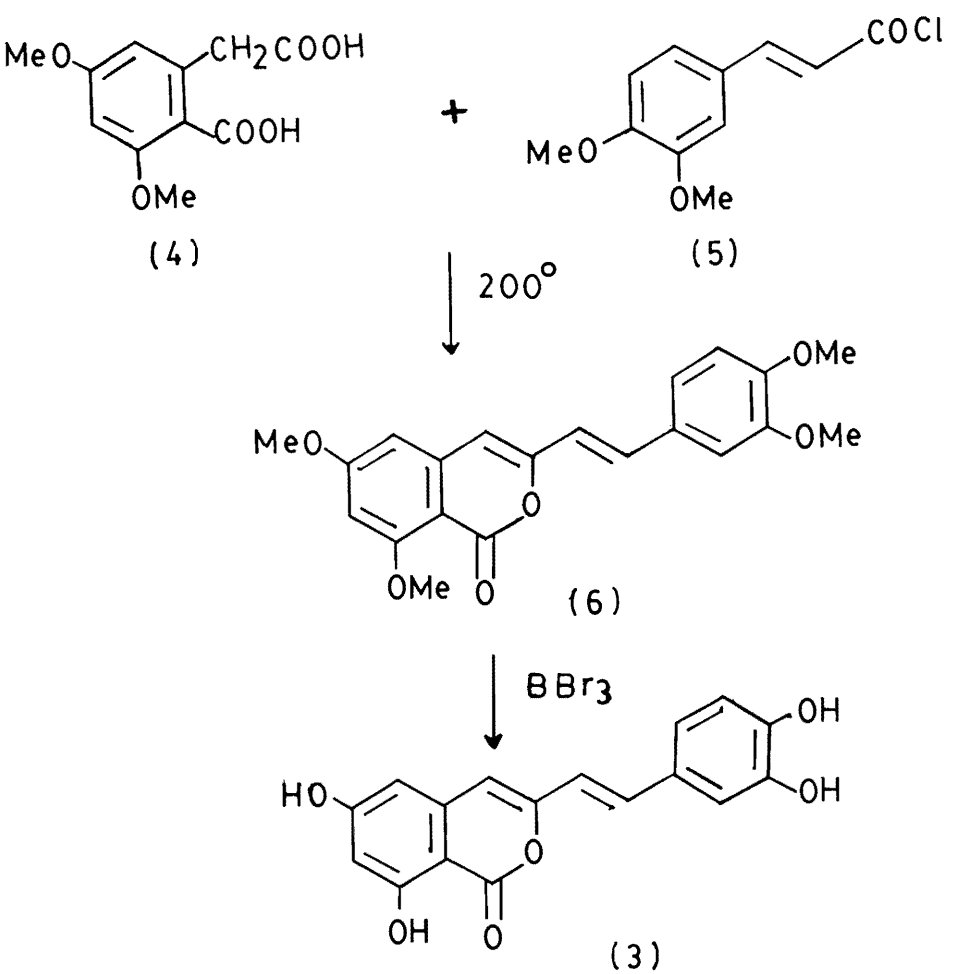

HO
OH
Ger
OH
O
O
(1)
HO
OH
R2
R1
OH
O
O
(2;R1=Ger,R2=H)
(3;R1=H,R2=OH)

Fig. 1


MeO
CH2COOH
COOH
OMe
(4)
+
COCl
MeO
OMe
(5)
200°
OMe
OMe
MeO
O
OMe
O
(6)
BBr3
OH
OH
HO
O
OH
O
(3)

Scheme

Table 1.

Synthetic (3)				Isolated (3) [1]			
δ(ppm) ($CDCl_3$)	Multiplicity	*J*(Hz)	Proton	δ(ppm) ($CDCl_3$)	Multiplicity	*J*(Hz)	Proton
6.47	1H, d	2.2	H-7	6.37	1H, d	2.0	H-7
6.51	1H, d	2.5	H-5	6.45	1H, d	2.0	H-5
6.61	1H, s	–	H-4	6.55	1H, s	–	H-4
6.75	1H, d	16.5	H-7′	6.72	1H, d	16.0	H-7′
6.90	1H, d	7.5	H-5′	6.86	1H, d	8.0	H-5
7.10	1H, dd	2.5, 9.1	H-6′	7.03	1H, dd	2.0, 8.1	H-6′
7.21	1H, d	2.1	H-2′	7.15	1H, d	2.1	H-2′
7.25	1H, d	16.0	H-8′	7.21	1H, d	16.0	H-8′

6,8-Dimethoxy-3-(3′,4′-dimethoxyphenylethenyl)isocoumarin (6)

Oxalyl chloride (5 ml, 0.072 mol) was added dropwise to a stirred solution of 3,4-dimethoxycinnamic acid (Aldrich, predominantly *trans*) (5.0 g, 0.024 mol) in dry benzene (20 ml). The solution turned yellow with vigorous effervescence and after 24 hours the benzene was evaporated. More benzene was added and the solution was evaporated; the process was repeated until the smell of oxalyl chloride was absent. The 3,4-dimethoxycinnamoyl chloride (**5**) residue was crystallized from ethyl acetate to give yellow crystals (4.9 g, 0.0216 mol, 90%).

A mixture of 3,5-dimethoxyhomophthalic acid (**4**) (0.6 g, 0.0025 mol) and the acid chloride (**5**), (2.35 g, 0.010 mol) was heated at 200°C in an oil bath for 5 hours and then refluxed for 1 hour with methanol (50 ml), to convert the excess of acid chloride into the corresponding ester. The residue was purified by thick layer chromatography and precipitated from petroleum ether:diethyl ether (4:1) to afford 6,8-dimethoxy-3-(3′,4′-dimethoxyphenylethenyl)isocoumarin (**6**) (0.51 g 0.0014 mol, 55%) as a semisolid.

IR (KBr): 1680 (lactonic carbonyl), 1602, 1584 (aromatic) cm^{-1}. PMR δ($CDCl_3$): 3.80(3H, s, OMe), 3.82(3H, s, OMe), 3.87(3H, s, OMe), 3.89(3H, s, OMe), 6.47(1H, d, J = 2.2 Hz, H-7), 6.51(1H, d, J = 2.2 Hz, H-5), 6.56(1H, s, H-4), 6.75(1H, d, J = 16.5 Hz, H-7′), 6.90(1H, d, J = 7.5 Hz, H-5′), 7.10(1H, dd, J_1 = 2.5 Hz, J_2 = 9 Hz, H-6′), 7.21(1H, d, J = 2, 1 Hz, H-2′), 7.25(1H, d, J = 16 Hz, H-8′)ppm. MS: *m/z*: 370, 369(M^+), 215(base), 178, 151. Analysis: *Calc.* for $C_{21}H_{20}O_6$: C 68.48, H 5.43; *Found:* C 68.59, H 5.72.

6.8-Dihydroxy-3-(3′,4′-dihydroxyphenylethenyl)isocoumarin (3)

A solution of boron tribromide in dichloromethane (2 ml, 1.0M) was added dropwise to a stirred solution of 6,8-dimethoxy-3-(3′,4′-dimethoxyphenylethenyl)isocoumarin (**6**) (0.74 g, 0.002 mol) in dry dichloromethane (5 ml) at 0°C under nitrogen and the mixture was heated under reflux for 2 hours. After cooling, the reaction mixture was poured into ice-water, and extracted with dichloromethane (3×30 ml). The concentrated residue was precipitated with methanol to afford 6,8-dihydroxy-3-(3′,4′-dihydroxyphenylethenyl)isocoumarin (**3**) (0.34 g, 0.001 mol, 54%) as a brownish amorphous powder.

IR (KBr): 3406, 3244, 1626 cm^{-1}. PMR δ($CDCl_3$): 6.47(1H, d, J = 2.2 Hz, H-7), 6.51(1H, d, J = 2.2 Hz, H-5), 6.61(1H, s, H-4), 6.75(1H, d, J = 16.5 Hz, H-7′), 6.90(1H, d, J = 7. 5 Hz, H-5′), 7.10(1H, dd, J_1 = 2.5 Hz, J_2 = 9 Hz, H-6′), 7.21(1H, d, J = 2.1 Hz, H-2′), 7.25(1H, d, J = 16 Hz, H-8′) ppm. MS: *m/z*: 313, 312(M^+), 177(base), 151.

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