One-Pot Synthesis of Unsymmetrically Substituted 2,4-Dialkylisoflavenes

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The trimethylsilyl derivative of formonometine reacts sequentially with two different organometallic derivatives to afford regiospecifically and with good yield 2,4-dialkylisoflavenes unsymmetrically substituted.

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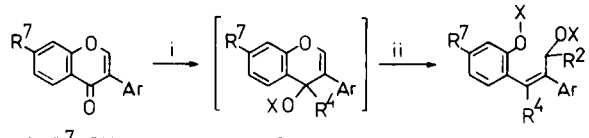
In previous works we have reported the synthesis of 2,4-disubstituted-2*H*-1-benzopyrans [1] from hydroxycynnamyl alcohols obtained by reaction of chromones and coumarins with organoaluminium derivatives in benzene or hexane [1-3]. Similarly, we have also showed that flavone reacts with Grignard derivatives, at low temperature, yielding a 4-chromenolic intermediate easily transformed into an unsymmetrically disubstituted benzopyran by adding an excess of a different alkylaluminium reagent, hydrolysis and acidic work-up [1].

The described protocol allowed one-pot synthesis of 2,4-dialkyl-4',7-dihydroxyisoflavenes with estrogenic activity [4] from isoflavones. We report now a versatile and highly efficient synthesis of 2,4-dialkylisoflavenes from the readily available formonometine (Table).

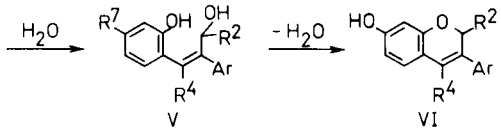
Scheme 1



I. R^7 = OH
II. R^7 = OSiMe

III
X = AlR_2, MgBr, Li

IV



V

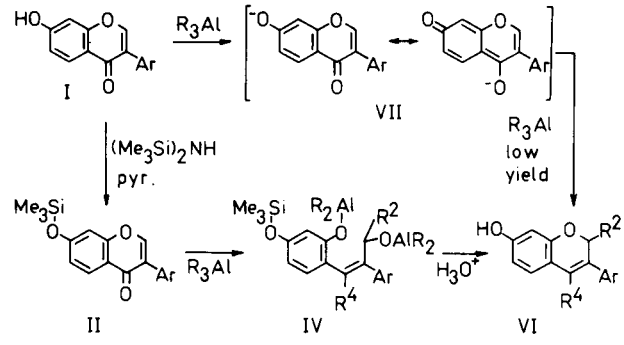
VI

i = R_3Al, RMgBr, RLi
ii = R_3Al

VIa. $R^2 = R^4$ = Et, Ar = p-C_6H_4-OCH_3
VIb. $R^2 = R^4$ = Me, Ar = p-C_6H_4-OCH_3
VIc. R^2 = Me, R^4 = Et, Ar = p-C_6H_4-OCH_3
VId. R^2 = Et, R^4 = Me, Ar = p-C_6H_4-OCH_3
VIe. R^2 = Et, R^4 = n-Bu, Ar = p-C_6H_4-OCH_3
VIf. R^2 = Me, R^4 = n-Bu, Ar = p-C_6H_4-OCH_3

The formonometine I reacts with triethyl- or trimethylaluminium to afford 2,4-diethyl- or 2,4-dimethyl-7-hydroxy-4-methoxyisoflavenes VI but with yields intolerably low (5-7%), recovering the starting material, probably as a consequence of the low solubility of I and its metallic complexes in benzene, or the formation of the unreactive conjugated base VII [5]. Otherwise, the reaction proceeds to completion, under the same experimental conditions, if trimethylsilyl derivative of formonometine II is used.

Scheme 2



I

VII

II

IV

VI

Although the best results in the cyclization process of 2(3-hydroxy-1-propenyl)phenols to 2*H*-1-benzopyrans were obtained with silicagel in refluxing xylene or mesytilene [1], now we have used an acidic work-up in the transformation of IV into VI because the hydrolysis, deprotection and cyclization occur in a single step [6]. In this way, VIa and VIb were synthesized in 55 and 58% yields respectively, after column chromatography and recrystallization.

The reaction of II with ethyllithium (molar ratio 1:2), at -10°, leads to an intermediate that, when treated with an equimolar amount of anhydrous acetone and then with a solution of trimethylaluminium in hexane, and acidic hydrolysis, yields the 2-methyl-4-ethylisoflavene VIc in excellent yield. In constrast, when organolithium was substituted by ethylmagnesium bromide the reaction failed to yield the desired products over a wide range of temperatures, and the final product was the ketone VIII resulting from the incorporation of two ethyl groups from the organometallic.

Although no attempts to establish the nature of the chromenolic intermediate were made, we propose the structure III because it afforded the isoflavilium salt IX after hydrolytic work-up.

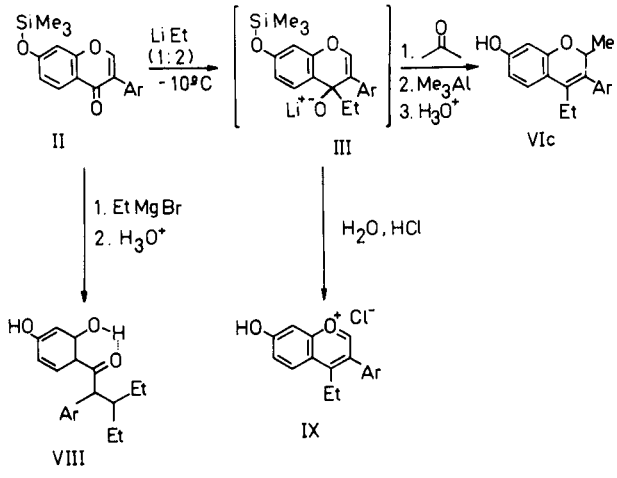
Table

Synthesis of Isoflavenes VI from Formonometines I or II
I or II → VII → IV → VI

Isoflavone	Organometallic	Solvent	Temperature (°C)	Isoflavene (%)
I R^7 = OH	i = ii = Et_3Al	toluene	0 [a,b]	VIa R^2 = R^4 = Et (5) [c]
I "	i = ii = Me_3Al	toluene	0 [a,b]	VIb R^2 = R^4 = Me (7) [c]
II R^7 = $OSiMe_3$	i = ii = Et_3Al	benzene	0 [b]	VIa R^2 = R^4 = Et (55)
II "	i = ii = Me_3Al	benzene	0 [b]	VIb R^2 = R^4 = Me (58)
II "	i = EtMgBr	ether	—5 [a]	
	ii = Me_3Al	benzene	0	— [d]
II "	i = ii = EtMgBr	ether	—5 [a,b]	— [d]
II "	i = EtLi	hexane	—20	
	ii = Me_3Al	tolune	0	VIc R^2 = Me, R^4 = Et (61)
II "	i = MeLi	ether	—20	
	ii = Et_3Al	benzene	0	VId R^2 = Et, R^4 = Me (59)
II "	i = BuLi	hexane	—20	
	ii = Et_3Al	toluene	0	VIe R^2 = Et, R^4 = *n*-Bu (48)
II "	i = BuLi	hexane	—20	
	ii = Me_3Al	toluene	0	VIf R^2 = Me, R^4 = *n*-Bu (66)

[a] Yields remained unchanged on a wide range of temperatures. [b] Only one organometallic used, and added in the first step of the process. [c] 90% of I was recovered unchanged. [d] The ketone VIII was obtained in high yield.

Scheme 3



The reactivity of organoaluminium derivatives decreases in ethereal solution, then, it is experimentally advantageous to avoid this solvent, and the reactions must be carried out in hexane or toluene whenever possible, or to change the solvent when ethereal solutions of an organometallic are employed (methyllithium). It is also important to use an excess of alkyllithium (molar ratio 1:2) [7] to obtain the total transformation of the starting material into the intermediate and avoid the formation of by-products.

EXPERIMENTAL

Melting points are uncorrected and determined on an open capillary tube. The ir spectra were determined on a Pye-Unicam SP-1100 spectrometer, and pmr spectra on a Varian T60A, at 60 MHz (δ from TMS). Elemental analysis were performed on a Perkin Elmer 240B analyzer.

7-Hydroxy-4'-methoxyisoflavone (I).

Synthesized (55%) by a described method (8) from α-(4-methoxyphenyl)-2,4-dihydroxyacetophenone and triethylorthoformate in pyridine-piperidine.

4'-Methoxy-7-trimethylsilyloxyisoflavone (II).

To a solution of 5 g of 7-hydroxy-4'-methoxyisoflavone (I) in 100 ml of anhydrous pyridine, under nitrogen, was slowly added 11 ml of redistilled hexamethyldisilazane. The solution was heated at 80° for 2 hours and then cooled to room temperature and the solvent and excess of hexamethyldisilazane removed under vacuum. The residual white crystals (6.4 g) were 95% pure (by pmr) and used without further purification; pmr (deuteriochloroform): 8.10 (d, 1H), 7.80 (s, 1H), 7.40 (d, 2H), 6.90 (d, 2H), 6.85 (d, 1H), 6.75 (s, 1H), 3.75 (s, 3H), 0.30 (s, 9H).

2,4-Diethyl-7-hydroxy-4'-methoxyisoflavene (VIa).

A solution of 4'-methoxy-7-trimethylsilyloxyisoflavone (II) (5.1 g, 15 mmoles) in 100 ml of anhydrous benzene were slowly (*ca.* 1.5 hours) added at 0°, to a stirred solution of triethylaluminium (6 ml, 45 mmoles) in 200 ml of the same solvent, under nitrogen. The solution was stirred for 24 hours at room temperature, then 40 ml of water was added and the mixture acidified with concentrated hydrochloric acid and stirred until the reaction was completed (the processes were monitored by tlc). The mixture was decanted, the aqueous layer extracted with ether, the organics washed with a solution of sodium bicarbonate and water, and dried over anhydrous magnesium sulfate. The solvents were removed under vacuum and the residue purified by column chromatography (silicagel:methylene chloride). The solid was recrystallized from hexane/-benzene, obtaining 2.57 g (55%) of white solid, mp 126-127°; ir (potassium bromide): cm^{-1} 3400, 1630; uv (ethanol): λ max (log ϵ) 209 (4.403), 228 (4.274), 290 (4.038), 312 (4.122); pmr (deuteriochloroform): 7.40-6.40 (m, 7H), 5.70 (s, 1H), 4.80 (q, 1H), 3.90 (s, 3H), 2.35 (q, 2H), 1.60 (m, 2H), 1.00 (t, 3H), 0.90 (t, 3H).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.49; H, 7.19.

2,4-Dimethyl-7-hydroxy-4'-methoxyisoflavene (VIb).

From 4'-methoxy-7-trimethylsilyloxyisoflavene and trimethylaluminium by the above described procedure there was obtained 2.45 g (58%) of

a white solid, mp 101-102° (lit [5] oil); ir (potassium bromide): cm^{-1} 3400, 1630; uv (ethanol): λ max (log ε) 212 (4.420), 230 (4.243), 296 (4.081), 312 (4.188); pmr (deuteriochloroform): 7.30-6.30 (m, 7H), 5.05 (q, 1H), 3.80 (s, 3H), 1.90 (s, 3H), 1.20 (d, 3H).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.41.

4-Ethyl-7-hydroxy-2-methyl-4'-methoxyisoflavene (VIc).

To a stirred solution of 7.1 g (21 mmoles) of II in 200 ml of toluene, under nitrogen, was dropped 34 ml of 1.2 *M* solution of ethyllithium in hexane (40.8 mmoles) at -20°. The temperature was allowed to rise to -10° for 3 hours, and then 14.7 ml (20 mmoles) of anhydrous acetone was added and the mixture stirred for 15 minutes at 0°. After that, 6 ml (63 mmoles) of trimethylaluminium was injected into the reaction and stirred at room temperature for 13 hours. After acidic hydrolysis, cyclization and purification as above described 3.8 g (61%) of VIc was obtained as a white solid, mp 127-128° (lit [4,5] oil); ir (potassium bromide): cm^{-1} 3400, 1630; uv (ethanol): λ max (log ε) 212 (4.421), 228 (4.274), 285 (4.064), 312 (4.117); pmr (deuteriochloroform): 7.40-6.30 (m, 7H), 5.00 (q, 1H), 3.80 (s, 3H), 2.35 (q, 2H), 1.25 (d, 3H), 1.00 (t, 3H).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.89; H, 6.91.

2-Ethyl-7-hydroxy-4-methyl-4'-methoxyisoflavene (VId).

Compound II (4.7 g, 14 mmoles) in 200 ml of anhydrous ether, under nitrogen was treated at -20° with 17.2 ml of 1.6 ethereal solution of methyllithium (28 mmoles). After 3 hours at -20° the excess of the organometallic was destroyed by addition of 14 mmoles of anhydrous acetone. The ether was distilled under vacuum and anhydrous benzene added, and then, 42 mmoles of triethylaluminium was injected at 0°. The hydrolysis, cyclization and column chromatography yielded 2.4 g (59%) of isoflavene VId as a white solid, mp 90-91°; ir (potassium bromide): cm^{-1} 3400, 1630; uv (ethanol): λ max (log ε) 215 (4.359), 231 (4.241), 293 (4.065), 316 (4.194); pmr (carbon tetrachloride): 7.30-6.30 (m, 7H), 4.80 (q, 1H), 3.80 (s, 3H), 1.90 (s, 3H), 1.50 (m, 2H), 0.90 (t, 3H).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.08; H, 6.88.

4-Butyl-2-ethyl-7-hydroxy-4'-methoxyisoflavene (VIe).

From 6.56 g (20 mmoles) of II and butyllithium and triethylaluminium as described for VIc there was isolated 3.24 g (48%) of isoflavene VIe as an unstable yellow oil (93% pure by pmr); ir (film): cm^{-1} 3400, 1640; pmr (carbon tetrachloride:acetone-d_6 1:1): 7.30-6.20 (m, 7H), 4.70 (m, 1H), 3.80 (s, 3H), 2.3 (m, 2H), 1.6-1.2 (m, 4H), 0.8 (m, 6H).

A specimen was derivatized as the acetate and purified by recrystallization from ethanol, white solid, mp 83-85°.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.61; H, 7.58.

4-Butyl-7-hydroxy-2-methyl-4'-methoxyisoflavene (VIf).

As described for VIe, 66% of an unstable yellow oil (95% pure by pmr); ir (film): cm^{-1} 3400, 1640; pmr (acetone-d_6): 7.30-6.30 (m, 7H), 4.95 (q, 1H), 3.80 (s, 3H), 2.30 (t, 2H), 1.25 (d, 3H), 1.40-1.10 (m, 4H), 0.80 (t, 3H).

An acetate was prepared, white solid, 76-77° (from ethanol).

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.19; H, 7.31.

2,4-Dihydroxyphenyl [2-Ethyl-1-(4'-methoxyphenyl)]butyl Ketone (VIII).

To a solution of 45 mmoles of ethylmagnesium bromide in 50 ml of ether, was slowly dropped, at -50°, 5.1 g (15 mmoles) of II in 100 ml of ether. The reaction mixture was allowed to rise to room temperature and stirred for 12 hours. After the corresponding acidic hydrolysis and purification by column chromatography (silicagel, dichloromethane) there was isolated 2.6 g (54%) of VIII as a yellow oil, bp 202-206°/0.1 mm; ir (film): cm^{-1} 3360, 1635, 1600; pmr (deuteriochloroform): 11.50 (s, 1H), 7.85 (d, 1H), 7.35 (d, 1H), 7.30 (s, 1H), 6.85 (d, 1H), 6.40 (d, 1H), 6.40 (s, 1H), 4.40 (d, 1H), 3.80 (s, 1H), 2.30 (m, 1H), 1.30 (m, 4H), 0.80 (t, 6H).

A 2,4-dinitrophenylhydrazone was prepared, orange solid, mp 181° dec (from ethanol).

Anal. Calcd. for $C_{26}H_{28}N_4O_7$: C, 61.41; H, 5.55; N, 11.02. Found: C, 61.30; H, 5.62; N, 11.22.

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[6] The hydrolysis and deprotection of IV under neutral conditions yields a mixture of V and silylated diol. Attempts to obtain V under more drastic hydrolytic conditions afforded a mixture of V and VI.

[7] The organolithium excess was destroyed by adding an equimolar amount of anhydrous acetone before the second organometallic compound.

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