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THE CHEMISTRY OF PENTAVALENT ORGANOBISMUTH REAGENTS. Part XII. SYNTHESIS OF ISOFLAVANONES AND 3-ARYL-4-HYDROXYCOUMARINS

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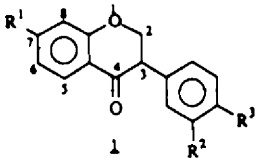
Abstract - The arylation of chroman-4-one and 4-hydroxycoumarin derivatives by pentavalent arylbismuth reagents has been carried out. Chroman-4-one gives the 3-diphenyl derivative, whereas 3-formyl and 3-oxalyl derivatives are phenylated to isoflavanones in moderate to high yields. Arylation of 4-hydroxycoumarins by various Bi(V) reagents gives rise to functionally substituted 3-aryl-4-hydroxycoumarins in high yields.

The isoflavanones, 3-aryl-4-hydroxycoumarins and their further elaborated structures, such as the pterocarpans and rotenoids, are an important group of biologically active natural products, possessing a common C-15 skeleton. While the isoflavanones 1 and 3-aryl-4-hydroxycoumarins 2 have exhibited limited biological activity, they are important synthetic precursors leading to the biologically active isoflavonoid derivatives.[1] The isoflavonoids, which are of limited taxonomic distribution, have oestrogenic, insecticidal, piscicidal and antifungal properties.[2] A number of synthetic routes have been devised with limited success for the synthesis of isoflavanones[3] and 3-aryl-4-hydroxycoumarins.[4]



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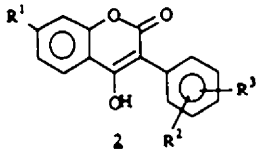

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The synthesis of both of these isoflavonoid structural types in good yields still remains unsatisfactory. Arylation α- to the carbonyl group of the chroman-4-one 3 and 4-hydroxycoumarin 4 skeletons is an obvious synthetic route to the isoflavanoid and the 3-aryl-4-hydroxycoumarins, respectively. The most satisfactory synthesis of isoflavanones, for example, is the palladium catalysed Heck arylation of chrom-3-en-4-ol acetates with arylmercury(II) compounds.[5] However, it requires the use of a stoichiometric amount of palladium acetate and of toxic arylmercury derivatives.

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Among the recently introduced arylation methods, two groups of organometallic compounds have emerged as particularly efficient aryl cation equivalents for the arylation of a wide variety of substrates under very mild conditions : the aryl-lead(IV) compounds studied by Pinhey,[6] and the arylbismuth(V) compounds.[7] Pentavalent organobismuth compounds are efficient arylating reagents for phenols, ketones, enols and other ambident anions, as well as for the O- and N-phenylation of alcohols, phenols, and amines.[7] As an extension of these studies towards the synthesis of natural products, we now report the application of these reagents to the direct arylation of the chroman-4-one 3 and 4-hydroxycoumarin 4 skeletons.

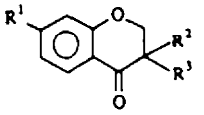
Arylation of the potassium enolate of chroman-4-one 3 with Ph_3BiCO_3 5 or Ph_3BiCl_2 6 led to modest yields of the C(3)-diphenyl derivative 7, and some monophenyl derivative 8, with

Bismuth Reagents

Ph_3BiCO_3 5	$Ph_4BiOTos$ 22	$Ph_3Bi(NO_3)_2$ 26
Ph_3BiCl_2 6	Ph_5Bi 23	$p\text{-}Tol_3Bi(OAc)_2$ 30
$Ph_3Bi(OAc)_2$ 21	$Ph_3Bi(OTos)_2$ 24	$(m\text{-}NO_2\text{-}C_6H_4)_3Bi(NO_3)_2$ 33

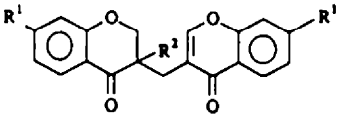
concomitant decomposition of 3. Variation of the reaction conditions failed to improve the selectivity of the arylation. Because of the higher acidity of C(3)-H in 8, enolate exchange favoured the formation of the second covalent arylbismuth enolate,[8] leading to the diphenyl compound 7. To stop the phenylation at the monophenylated stage, the most obvious way was to replace one of the acidic protons at C(3) by an easily removable electron-withdrawing group[9] which would further activate that position towards enolate formation. Since most natural isoflavanones possess a C(7) oxygen substituent the arylation studies were then performed with 7-substituted chroman-4-ones. Various attempts to prepare the 3-carbethoxy derivative of 7-benzyloxychroman-4-one 9 led to complex mixtures.

Substituted Chroman-4-ones



N°	R^1	R^2	R^3
3	H	H	H
7	H	Ph	Ph
8	H	Ph	H
9	OCH_2Ph	H	H
10	OCH_3	H	H
11	OCH_2Ph	CHO	H
12	OCH_3	CHO	H
13	OCH_2Ph	Ph	Ph
14	OCH_3	Ph	Ph
15	OCH_2Ph	Ph	H
16	OCH_3	Ph	H
20	OCH_2Ph	$CO\text{-}CO_2Et$	H

However, sodium methoxide catalysed aldol condensation of 9 and 10 with ethyl formate afforded satisfactory yields of the 7-benzyloxy and 7-methoxy-3-formylchroman-4-one 11 and 12. The phenylation of 11 and 12 was attempted under a variety of conditions. Because of the relative instability of 11 and 12, the diphenylated products 13 and 14 were produced in high yield, following in situ deformylation. The best yield of 7-benzyloxyisoflavanone 15 was only 32%, and for the 7-methoxy analogue 16, only 26%. Moreover, in the arylation reaction of 11, two minor products 17 and 18 were also observed. Dimer 17 arose by an aldol condensation between 11



17 R^1 = $PhCH_2O$; R^2 = H
18 R^1 = $PhCH_2O$; R^2 = Ph
19 R^1 = CH_3O ; R^2 = H

and its enolate, followed by decarbonylation, dehydration and subsequent isomerisation, while product 18 arose by a direct phenylation of 17. In the arylation of 12, only the dimer 19 was observed. As an alternative activating group, oxalyl derivative 20, a stable, crystalline compound was prepared by condensation of 9 with diethyl oxalate. Whilst hydrolysis of the oxalyl group did not occur with 20, high yields of diphenylated product 13 were again observed for both tri- and tetra-phenylbismuth reagents 21 and 22. Whereas reaction of 22 required basic conditions, triphenylbismuth diacetate 21 reacted even under neutral conditions to yield the diphenyl derivative 13. Pentaphenylbismuth 23 is known to react with a wide variety of substrates under neutral conditions, and particularly with enolic β-dicarbonyl compounds.[10] Thus, reaction of 23 with 20 led to a good yield of the monophenylated derivative 15 (58% at room temperature). Under these reaction conditions, the oxalyl protecting group was also lost, after phenylation took place. A small amount of the diphenyl derivative 13 was obtained. However, conducting the reaction at -23°C under strictly neutral conditions, a near quantitative yield of 7-benzyloxyisoflavanone 15 was directly obtained (88%), with only 3% of the diphenyl derivative 13. In spite of their relative instability, enolic substrates 11 and 12 reacted with 23 to afford high yields of the corresponding isoflavanones 15 and 16. Again, hydrolysis of the formyl group was not necessary, as it was lost under the reaction conditions. This synthetic route, utilising pentaphenylbismuth, provides a general method for the synthesis of A-ring substituted isoflavanones in high yield. However, most of the biologically active isoflavanoids also possess a substituent in the B-ring. Theoretically, substituted pentaarylbismuth would be required. Unfortunately, a limited number of such compounds is known, and none of them is suitable for further elaboration to variously substituted isoflavanones.[11]

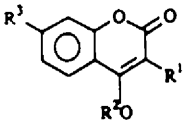
An alternative synthetic approach to the synthesis of B-ring substituted isoflavonoids would involve the action of pentavalent organobismuth reagents on 4-hydroxycoumarin derivatives. Pentaphenylbismuth 23, triphenylbismuth dichloride 6 and ditosylate 24 were reacted with 4-hydroxycoumarin 4 to give very low yields of the monophenylated derivative 25. However, triphenylbismuth dinitrate 26 realised a relatively good phenylation of 4, under basic conditions, to give 4-hydroxy-3-phenylcoumarin 25 (55%). Eventually, triphenylbismuth diacetate 21 reacted with 4 under basic conditions to provide a high yield of 25 (81%).

Table 1. Phenylation of Chroman-4-one Derivatives

Substrate	Bi^V Reagent (eq.)	Reaction Conditions[a] (eq.)	Products (%)
3	5 (3)	THF, KH (3), reflux, 12h	7 (34)
3	6 (3)	CH_2Cl_2, KH (3), reflux, 12h	7 (38)
3	5 (1.1)	CH_2Cl_2, KH (3), rt, 72h	7 (17), 8 (15)
3	6 (1.1)	THF, KH (3), rt, 72h	7 (20), 8 (22)
11	5 (1.2)	THF, KH (3), rt, 7h	13 (40), 15 (14)
11	5 (1.2)	THF, BTMG (3.9), rt, 15h	13 (13), 15 (10), 17 (17)
11	6 (1.5)	THF, BTMG (1.2), rt, 3h	13 (14), 15 (32), 17 (5)
11	6 (1.5)	THF, BTMG (1.2), 18C6, rt, 36h	13 (15), 15 (30), 17 (2), 18 (2)
11	23 (1)	THF, -23°C, 1h	13 (7), 15 (84)
12	5 (1.1)	THF, BTMG (1.5), rt, 2h	14 (10), 16 (4), 19 (40)
12	6 (1.1)	THF, BTMG (1.1), rt, 4h	14 (14), 16 (25), 19 (13)
12	23 (1)	THF, -23°C, 1h	14 (9), 16 (79)
20	21 (1.1)	CH_2Cl_2, dark, reflux, 4h	13 (25), 15 (21), 20 (41)
20	22 (1.4)	THF, BTMG (2.1), rt, 21h	13 (37), 15 (23), 20 (26)
20	23 (1.5)	THF, rt, 3h	13 (11), 15 (58), 20 (6)
20	23 (1)	THF, -23°C, 2h	13 (3), 15 (88)

a) rt is room temperature; 18C6 is dicyclohexyl-18-crown-6.

Substituted 4-hydroxycoumarins



N°	R^1	R^2	R^3
4	H	H	H
25	Ph	H	H
27	H	Ph_3XBi	H
28	H	H	CH_3O
29	Ph	H	CH_3O
31	4-CH_3-C_6H_4	H	H
32	4-CH_3-C_6H_4	H	CH_3O
34	3-O_2N-C_6H_4	Ac	H
35	3-Cl-C_6H_4	Ac	H
36	3-AcO-C_6H_4	Ac	H

The striking influence of the leaving group intervening in the formation of the covalent coumarinoxybismuth intermediate 27 is noteworthy. Moreover, only the monophenylated product was obtained. An even higher yield of 25 was obtained with triphenylbismuth diacetate, when the reaction of 4 with 21 was performed in refluxing THF or CH_2Cl_2 in the dark, under neutral conditions. As opposed to the reaction of 21 with the enolic substrate 20 resulting in the bis-C-phenyl derivative, only the mono-C-phenyl derivative 25 was obtained under these neutral

conditions. Although a similar C-phenylation reaction was observed previously in the case of ethyl 2-oxocyclohexanecarboxylate,[12] such a reaction was rather unexpected on the basis of our recently described O-arylation reaction of a variety of substrates (such as phenols, enols and alcohols) by triarylbismuth diacylates.[13] This reaction was also applied to 7-methoxy analogue 28 affording 29. Again, the generality of this reaction is limited by the availability of the triarylbismuth diacetates. Thus, reagent 30 gave the coumarins 31 and 32 in good yields.

Table 2. Arylation of 4-Hydroxycoumarin Derivatives

Substrate	Bi^V Reagent (eq.)	Reaction Conditions (eq.)	Products (%)
4	6 (1.65)	THF, KH (3), reflux, 67h	4 (46), 25 (25)
4	26 (1.10)	THF, BTMG (1.2), rt, 23h	4 (25), 25 (55)
4	21 (1.05)	THF + CH_2Cl_2, BTMG (1.2), rt, 60h	4 (8), 25 (81)
4	21 (1.1)	CH_2Cl_2, dark, reflux, 16h	4 (3), 25 (92)
4	30 (1.25)	CH_2Cl_2, dark, reflux, 19h	4 (8), 31 (85)
4	33 (1.05)	THF, BTMG (1.2), rt, 96h	34 (83)
28	21 (1.45)	CH_2Cl_2, dark, reflux, 43h	28 (5), 29 (82)
28	30 (1.45)	CH_2Cl_2, dark, reflux, 45h	28 (7), 32 (80)

Recent studies on the comparative migratory aptitude of aryl groups in the arylation of phenols and enols by pentavalent arylbismuth reagents have shown that nitro substituted aryl groups migrate much faster than a phenyl or anisyl groups.[14] Under basic conditions, triphenylbismuth dinitrate proved to be the most efficient arylating agent for 4-hydroxycoumarin. Accordingly, the tri-m-nitrophenyl derivative 33 would be expected to show an even superior arylating activity. When this reagent was reacted with 4-hydroxycoumarin under basic conditions, and the reaction mixture acetylated, 4-acetoxy-3-(3'-nitrophenyl)-coumarin 34 was obtained in 83% yield. This compound was further functionalised. A variety of reducing agents (Raney nickel, titanium(II) chloride, titanium(III) chloride, iron-acetic acid) were tried without success in the attempted reduction of 4-acetoxy-3-(3'-nitrophenyl)-coumarin to the corresponding amine. However, reduction of 34 occurred on heating at 50°C in concentrated HCl for 12 hrs in the presence of tin(II) chloride. The amine salt was diazotised *in situ* by sodium nitrite. Replacement of the diazonium salt by a hydroxyl group followed by addition of water to the cold diazonium solution and heating at 70°C for 4 hrs. Acetylation of the reaction mixture with acetic anhydride/pyridine afforded two products, 4-acetoxy-3-(3'-chlorophenyl)-coumarin 35 (27%) and 4-acetoxy-3-(3'-acetoxyphenyl)-coumarin 36 (61%). The synthesis of a 3-aryl-4-hydroxycoumarin suitably derivatised for further modification was therefore realized.

These studies have shown that proper choice of the organobismuth reagent and of the reaction conditions can lead to high yields of selectively monophenylated derivatives, a reaction which was currently difficult to perform with organobismuth reagents and impossible with organolead compounds.[15] Further work is now under progress to elaborate these isoflavanone derivatives.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on Perkin-Elmer R12 or R12B and Varian EM-360 (60 MHz) spectrometers or with a Jeol PFT 100L (100 MHz) instrument for solutions in $CDCl_3$ with TMS as internal standard, unless otherwise stated. 270 MHz ^{1}H-NMR and 67.8 MHz ^{13}C-NMR were recorded on a Jeol JNM-GX 270 FT instrument. IR spectra were recorded on Perkin-Elmer 283B or 297 apparatus. U.V. spectra were measured on a Pye-Unicam SP8-400, Perkin-Elmer 124, 558 or Lambda 5 spectrophotometers. Mass spectra were recorded on a VG micromass 7070 H spectrometer. All solvents and reagents were purified and dried by standard techniques. Chromatographic separations were performed using Merck Kieselgel 60 GF-254 (Preparative t.l.c.), Merck Kieselgel 60-H (Column chromatography at atmospheric pressure or under light pressure). Ether refers to diethyl ether. KH was a 35% suspension in mineral oil.

Preparation of Organobismuth Reagents

Triphenylbismuth carbonate 5, triphenylbismuth dichloride 6, triphenylbismuth diacetate 21, tetraphenylbismuthtoluene-p-sulphonate 22, pentaphenylbismuth 23, triphenylbismuth ditoluene-p-sulphonate 24 were prepared by literature methods as previously reported.[9]

Triphenylbismuth Dinitrate 26

A solution of fuming nitric acid (1.25 g, d 1.52) in anhydrous methylene dichloride (50 ml) was added dropwise to a vigorously stirred suspension of triphenylbismuth carbonate (5 g) in anhydrous methylene dichloride (75 ml). The reaction mixture was stirred for a further 30 min. The volume of methylene dichloride was reduced *in vacuo* and an excess of ether added. The precipitate was filtered, washed with water, ether and crystallized (methylene dichloride-ether) to give 26, as needles (4.75 g, 84%), m.p. 159-161°C, lit.[16] 148°C. (Found: C, 38.50; H, 2.51; N, 5.16. Calc. for $C_{18}H_{15}BiN_2O_6$: C, 38.22; H, 2.66; N, 4.96%).

Tri-m-nitrophenylbismuth Dinitrate 33

26 (2.5 g) was added to fuming nitric acid (25 g, d 1.52) which had been cooled to -15°C. The resulting solution was stirred at -15°C for 10 min, and then at room temperature for 22 hrs. The solution was cautiously added to ice-water (150 ml). The precipitate was filtered, washed with water, hexane and crystallized (acetone-hexane) to yield 33 as pale green needles (2.98 g, 96%), m.p. 145-147°C, lit.[17] 145°C. (Found: C, 31.25; H, 1.59; N, 9.52. Calc. for $C_{18}H_{12}BiN_5O_{12}$: C, 30.92; H, 1.72; N, 10.01%).

Tri-p-tolylbismuth Diacetate 30

To a well stirred suspension of tri-p-tolylbismuth carbonate[10] (1.15 g) in methylene dichloride (10 ml) was added dropwise at room temperature a solution of acetic acid (1.20 ml) in methylene dichloride (6 ml). After 15 min, the volume of the homogeneous reaction mixture was reduced to ca. 6 ml. An excess of ether was added and the precipitate filtered and crystallized[18] (methylene dichloride-hexane) to yield 30 as fine needles (1.03 g, 81%), m.p. 159-161°C, lit. 162°C.

Preparation of Oxygen Heterocycles

7-Benzyloxychroman-4-one 9 (m.p. 101-103°C, lit.[19] 103-104°C), 7-methoxychroman-4-one 10 (m.p. 52-54°C, lit.[20] 52-54°C), 3-formyl-7-methoxychroman-4-one 12 (m.p. 99-100°C, lit.[22] 100-101°C) and 4-hydroxy-7-methoxycoumarin 28 (m.p. 254-256°C, lit.[22] 256°C) were prepared by literature methods.

7-Benzyloxy-3-formylchroman-4-one 11

A solution of 9 (1.07 g) in anhydrous benzene (13 ml) was added dropwise to a cooled (0°C) solution of sodium methoxide (0.68 g) and ethyl formate (2.78 g) in anhydrous benzene (20 ml). The mixture was vigorously stirred for 1 hr. After acidification (H_2SO_4, 30 ml of a 2M solution), the benzene solution was extracted with aqueous 0.5M sodium carbonate (10x10 ml). The alkali extracts were acidified and the precipitate was filtered, washed with water and dried. After crystallization (hexane-ether), 11 was obtained as plates (0.88g, 74%), m.p. 112-113°C, ν_{max} ($CHCl_3$) 1610 cm^{-1}; λ_{max} (MeOH) 308(7691), 276(13791), and 214(27935) nm; δ ($CDCl_3$) 13.80 (1H, br.s, OH), 7.94 (1H, d, J 8.7 Hz, 5-H), 7.64 (1H, s, 3α-H), 7.49 (5H, s, Ph), 6.78 (1H, dd, J 8.7 Hz and 2.6 Hz, 6-H), 6.60 (1H, d, J 2.6 Hz, 8-H), 5.15 (2H, s, O-CH_2Ph), and 4.90 (2H, s, 2-CH_2); m/z 282 (M^+, 77), 254(15), 91(100), and 65(24) (Found: C, 71.96; H, 4.80. $C_{17}H_{14}O_4$ requires C, 72.36; H, 4.96%).

Ethyl ester of 7-Benzyloxy-4-oxochromanglyoxylic Acid 20

A solution of freshly distilled diethyl oxalate (2.64 g) in anhydrous toluene (10 ml) was added dropwise to a vigorously stirred solution of sodium ethoxide (2.93 g) and 9 (3.0 g) in anhydrous toluene (30 ml) under an atmosphere of argon at room temperature. After stirring for

21 h, the mixture was acidified (2M H_2SO_4, 60 ml). The toluene layer was exhaustively extracted with water (4x25 ml), followed by 0.5M aqueous sodium carbonate (4x30 ml). The combined aqueous extracts were quickly acidified. The yellow precipitate was filtered, washed with water, dried and crystallized (ethanol-hexane) to yield 20 as yellow plates (3.16 g, 76%). m.p. 109-110°C, ν_{max} ($CHCl_3$) 1723 and 1616 cm^{-1}; λ_{max} ($CHCl_3$) 370(12265) and 308(6736) nm; δ_H ($CDCl_3$, 270 MHz) 15.66 (1H, br.s, OH), 7.84 (1H, d, J 8.79 Hz, 5-H), 7.38 (5H, s, Ph), 6.69 (1H, dd, J 8.79 Hz and 2.20 Hz, 6-H), 6.47 (1H, d, J 2.2 Hz, 8-H), 5.38 (2H, s, OCH_2Ph), 5.09 (2H, s, 2-CH_2), 4.38 (2H, q, J 6.9 Hz, OCH_2), and 1.40 (3H, t, J 6.9 Hz, $-CH_3$); δ_C ($CDCl_3$) 185.39 (s, C-3a), 165.97 (s, C-4), 163.26 (s, C-7), 162.39 (s, C-9), 159.72 (s, C-3a), 135.68 (s, C-12), 128.90 (d, C-5), 128.82 (d, C-13, C-17), 128.47 (d, C-15), 127.58 (d, C-14, C-16), 114.16 (s, C-10), 111.43 (d, C-6), 107.65 (s, C-3), 101.82 (d, C-8), 70.49 (t, C-11), 66.14 (t, C-2), 62.52 (t, C-3γ, CH_2), and 14.14 (q, C-3ε, CH_3); m/z 354 (M^+, 14), 279(14), 252(14), and 91(100) (Found: C, 66.58; H, 4.92. $C_{20}H_{18}O_6$ requires C, 66.81; H, 5.08%).

Phenylation of Chroman-4-one 3

a) With Ph_3BiCO_3 5 (3 eq.) : A suspension of 3 (0.50 g), 5 (5.07 g) and potassium hydride (0.54 g) in anhydrous THF (30 ml) was stirred under reflux under nitrogen for 12 h. The mixture was filtered through Celite, THF distilled off, and the residue purified by column chromatography (eluant: hexane-chloroform-methanol 40:20:1) and crystallized (methanol) to yield 3,3-diphenylchroman-4-one 7 as needles (0.34 g, 34%), m.p. 129-131°C, lit.[23] 127-128°C.

b) With Ph_3BiCl_2 6 (3 eq.) : A reaction as above performed in anhydrous methylene dichloride (25 ml) with 3 (0.30 g), 6 (3.62 g) and KH (0.24 g) afforded 7 (0.23 g, 38%).

c) With Ph_3BiCO_3 5 (1.1 eq.) : A suspension of 3 (0.25 g), 5 (3.71 g) and KH (0.20 g) in anhydrous methylene dichloride (10 ml) was stirred at room temperature under nitrogen for 72 h. The mixture was filtered through Celite, the solvent distilled off and the residue purified by column chromatography (eluant: ether gradient in hexane) afforded 7 (0.086 g, 17%) and 8 which crystallized (methanol) as plates (0.056 g, 15%), m.p. 77°C, lit.[24] 77°C.

d) With Ph_3BiCl_2 6 (1.1 eq.) : A reaction as above performed in anhydrous THF (20 ml) with 3 (1 g), 6 (4 g) and KH (1.08 g) gave 7 (0.40 g, 20%) and 8 (0.33 g, 22%).

Phenylation of 7-Benzyloxy-3-formylchroman-4-one 11

a) With Ph_3BiCO_3 5 and KH : A suspension of 11 (0.125 g), 5 (0.261 g) and KH (0.052 g) in anhydrous THF (5 ml) was stirred at room temperature under an atmosphere of argon for 7 h. The mixture was filtered through Celite, the solvent distilled off and the residue fractionated by column chromatography (eluant: hexane-ether 3:2) to afford 7-benzyloxy-3,3-diphenylchroman4-one 13 (0.072 g, 40%) as a solid, m.p. 143-144°C, ν_{max} ($CHCl_3$) 1680 and 1626 cm^{-1}; λ_{max} (MeOH) 323(9730), 287(17075), and 230(42687) nm; δ ($CDCl_3$) 7.95 (1H, d, J 8.98 Hz, 5-H), 7.38-7.22 (15H, m, Ph), 6.63 (1H, dd, J 8.98 Hz and 2.38 Hz, 6-H), 6.43 (1H, d, J 2.38 Hz, 8-H), 5.02 (2H, s, $-OCH_2Ph$), and 4.85 (2H, s, O-CH_2); m/z 406 (M^+, 35), 329(10), 226(66), 180(64), 165(17), and 91(100)[2] (Found: C, 82.78; H, 5.43. $C_{28}H_{22}O_3$ requires C, 82.79; H, 5.42%), and 7-benzyloxyisoflavanone 15 (0.021 g, 14%) as a solid, m.p. 129-131°C, lit.[3c] 130-131°C.

b) With Ph_3BiCO_3 5 and BTMG : A reaction as above performed with 11 (0.122 g), 5 (0.281 g) and BTMG (0.288 g) stirred for 15 h afforded after work-up 13 (0.024 g, 13%), 15 (0.014 g, 10%), and 7,7'-dibenzyloxy-2,3-dihydro-3,3'-methylene-bischroman-4-one 17 (0.038 g, 17%), m.p. 166-167°C (methanol-benzene), ν_{max} (KBr) 1672, 1632, and 1606 cm^{-1}; λ_{max} ($CHCl_3$) 302(31769), 268(41730), and 244(39653) nm; δ ($CDCl_3$, 270 MHz) 8.11 (1H, d, J 8.79 Hz, 5'-H), 7.86 (1H, s, 2'-H), 7.81 (1H, d, J 8.79 Hz, 5-H), 7.45-7.32 (10H, m, 2Ph), 7.03 (1H, dd, J 8.97 Hz and 2.38 Hz, 6'-H), 6.87 (1H, d, J 2.38 Hz, 8'-H), 6.63 (1H, dd, J 8.98 Hz and 2.38 Hz, 6-H), 6.45 (1H, d, J 2.38 Hz, 8-H), 5.13 (2H, s, $-OCH_2Ph'$), 5.05 (2H, s, OCH_2Ph), 4.61-4.17 (2H, m, OCH_2), 3.13-3.08 (1H, m, 3-H), and 2.99 -2.64 (2H, m, CH_2); m/z 518 (M^+, 8), 427(4), 266(21), 253(72), and 91(100) (Found: C, 76.58; H, 5.05. $C_{33}H_{26}O_6$ requires C, 76.47; H, 5.02%).

c) With Ph_3BiCl_2 6 : A reaction as above performed with 11 (0.30 g), 6 (0.77 g), and BTMG (0.22 g), stirred for 1 h afforded after work-up 13 (0.060 g, 14%), 15 (0.11 g, 32%) and 17 (0.027 g, 5%).

d) With Ph_3BiCl_2 6 and 18-crown-6 : A reaction as above performed with 11 (1 g), 6 (2.71 g), dicyclohexyl-18-crown-6 (0.15 g) and BTMG (0.726 g) stirred for 56 h yielded 13 (0.11 g, 15%), 15 (0.18 g, 30%), 17 (0.019 g, 2%) and 7,7'-dibenzyloxy-2,3-dihydro-3-phenyl-3,3'-methylene-bischroman-4-one 18 (0.018 g, 2%), m.p. 149-150°C (methanol-benzene), ν_{max} (KBr) 1673, 1632, and 1605 cm^{-1}; λ_{max} ($CHCl_3$) 305(20386), 277(28118), and 149(26010) nm; δ ($CDCl_3$, 270 MHz) 8.02 (1H, d, J 8.79 Hz, 5'-H), 7.78 (1H, d, J 8.79 Hz, 5-H), 7.47 (1H, s, 2'-H), 7.39-7.15 (15H, m, 3Ph), 6.95 (1H, dd, J 8.97 Hz and 2.38 Hz, 6'-H), 6.74 (1H, d, J 2.38 Hz, 8'-H), 6.49 (1H, dd, J 8.89 Hz and 2.38 Hz, 6-H), 6.24 (1H, d, J 2.20 Hz, 8-H), 5.04 (2H, s, OCH_2-Ph'), 5.03 (1H, d, J 12.64 Hz, H_{2A} or H_{2B}), 4.89 (2H, s, O-CH_2-Ph), 4.36 (1H, d, J 12.64 Hz, H_{2B} or H_{2A}), 3.16 (1H, d, J 14.10 Hz, H_{11A} or H_{11B}), and 2.96 (1H, d, J 14.10 Hz, H_{11B} or H_{11A}); m/z 594 (M^+, 7), 503(8), 368(7), 329(100), 277(12), and 91(69) (Found: C, 78.40; H, 5.09. $C_{39}H_{30}O_6$ requires C, 78.80; H, 5.05%).

a) With Ph_5Bi 20 : A solution of 11 (0.050 g) and 20 (0.105 g) in anhydrous THF (1 ml) was stirred at -23°C under an atmosphere of argon for 1 h. THF was distilled off and preparative t.l.c. of the residue (eluant: methylene dichloride-hexane 9:1) afforded 13 (0.005 g, 7%) and 15 (0.049 g, 84%).

Phenylation of 7-Methoxy-3-formylchroman-4-one 12

a) With Ph_3BiCO_3 5 and BTMG : A reaction performed as for 11 with 12 (0.4 g), 5 (1.10 g) and BTMG (0.5 g) in THF (15 ml) stirred for 2 h at room temperature, afforded 3,3-diphenyl-7-methoxychroman-4-one 14 (0.066 g, 10%) as plates, m.p. 151-152°C (methanol-hexane), ν_{max} (KBr) 1664 and 1606 cm^{-1}; λ_{max} (MeOH) 314(8710), 276(15034), and 208(37421) nm; δ ($CDCl_3$, 270 MHz) 7.86 (1H, d, J 8.98 Hz, 5-H), 7.26-7.15 (10H, m, 2Ph), 6.48 (1H, dd, J 8.98 Hz and 2.38 Hz, 6-H), 6.26 (1H, d, J 2.38 Hz, 8-H), 4.78 (2H, s, $-OCH_2-$), and 3.70 (3H, s, OCH_3); m/z 330 (M^+, 51), 253(16), 180(100), 165(34), 150(82), and 122(10) (Found: C, 79.83; H, 5.44. $C_{22}H_{18}O_3$ requires C, 80.01; H, 5.45%), and 7-methoxyisoflavanone 16 as fine needles (0.020 g, 4%), m.p. 92-93°C (methanol), lit.[3d] 92°C, and 2,3-dihydro-7,7'-dimethoxy-3,3'-methylene-bischromen-4-one 19 (0.294 g, 40%), m.p. 173-175°C (ether-hexane), lit.[21] 174-175°C.

b) With Ph_3BiCl_2 6 : A reaction as above performed with 12 (0.50 g), 6 (1.38 g) and BTMG (0.47 g) stirred for 4 h at room temperature, afforded 14 (0.11 g, 14%), 16 (0.15 g, 25%), and 19 (0.112 g, 13%).

c) With Ph_5Bi 23 : A reaction performed as for 11 with 12 (0.1 g) and 23 (0.289 g) gave 14 (0.015 g, 9%), and 16 (0.097 g, 79%).

Phenylation of the Ethyl Ester of 7-Benzyloxy-4-oxochromanglyoxylic Acid 20

a) With $Ph_3Bi(OAc)_2$ 21 : A suspension of 20 (0.10 g) and 21 (0.17 g) in anhydrous methylene dichloride (6 ml) was stirred under reflux under an atmosphere of argon in the dark for 4 h. The reaction mixture was filtered through Celite, and the organic solvent distilled off. Preparative t.l.c. of the residue (eluant: methylene dichloride-hexane 3:2) afforded 13 (0.029 g, 25%), 15 (0.019 g, 21%) and unreacted 20 (0.041 g, 41%).

b) With $Ph_3BiOTos$ 22 : A solution of 20 (0.20 g), 22 (0.54 g) and BTMG (0.20 g) in anhydrous THF (8 ml) was stirred at room temperature under an atmosphere of argon for 21 h to afford, after work-up and preparative t.l.c., 13 (0.084 g, 37%), 15 (0.043 g, 23%) and 20 (0.053 g, 26%).

c) With Ph_5Bi 23 at room temperature : A solution of 20 (0.2 g) and 23 (0.50 g) in anhydrous THF (5 ml) was stirred at room temperature under an atmosphere of argon for 3 h. Work-up and preparative t.l.c. afforded 13 (0.026 g, 11%), 15 (0.108 g, 58%) and 20 (0.013 g, 6%).

d) With Ph_5Bi 23 at -23°C : A reaction as above with 20 (0.15 g) and 23 (0.25 g) performed at -23°C for 2 h afforded 13 (0.006 g, 3%) and 15 (0.123 g, 88%).

Arylation of 4-Hydroxycoumarin 4

a) With Ph_3BiCl_2 6 : A solution of 4 (0.25 g), 6 (1.31 g) and KH (0.58 g) in anhydrous THF (28 ml) was stirred under reflux under an atmosphere of argon for 67 h. The mixture was filtered through Celite and the solvent distilled off. Column chromatography (eluant: ether-hexane 3:1) afforded 4-hydroxy-3-phenylcoumarin 25 (0.091 g, 25%) as a solid which crystallized as needles (methanol-benzene), m.p. 236-237°C, lit.[4c] 239°C, and 4 (0.115 g, 46%).

b) With $Ph_3Bi(NO_3)_2$ 26 : A mixture of 4 (0.132 g), 26 (0.498 g) and BTMG (0.275 g) in anhydrous THF (12 ml) was stirred at room temperature under an atmosphere of argon for 23 h. Work-up and preparative t.l.c. (eluant: $CHCl_3$-methanol-H_2O 10:1:0.1) afforded 25 (0.106 g, 55%), and 4 (0.033 g, 25%).

c) With $Ph_3Bi(OAc)_2$ 21 under basic conditions : A reaction as above performed with 4 (0.15 g), 21 (0.542 g) and BTMG (0.317 g) in a mixture of anhydrous methylene dichloride (10 ml) and anhydrous THF (10 ml) was stirred at room temperature for 60 h. Work-up and preparative t.l.c. afforded 25 (0.178 g, 81%), and 4 (0.012 g, 8%).

d) With $Ph_3Bi(OAc)_2$ 21 under neutral conditions : A suspension of 4 (0.162 g) and 21 (0.615 g) in anhydrous methylene dichloride (15 ml) was stirred under reflux under an atmosphere of argon for 16 h. Work-up and preparative t.l.c. as above afforded 25 (0.22 g, 92%), and 4 (0.004 g, 3%).

e) With $p\text{-Tol}_3Bi(OAc)_2$ 30 : A reaction as above performed with 4 (0.11 g) and 30 (0.510 g) in anhydrous methylene dichloride (10 ml) stirred under reflux for 19 h afforded after work-up and preparative t.l.c. (eluant: $CHCl_3$-MeOH-H_2O 10:1:0.1) 4-hydroxy-3-p-tolylcoumarin 31 (0.145 g, 85%), as needles, m.p. 225-226°C (methanol), lit.[25] 226°C, and 4 (0.009 g, 8%).

f) With $(m\text{-}NO_2\text{-}C_6H_4)_3Bi(NO_3)_2$ 33 : A solution of BTMG (2.79 g) in anhydrous THF (8 ml) was added dropwise over a 1 h period to an ice-cooled (0°C) solution of 4 (1.32 g) and 33 (6 g) in anhydrous THF (16 ml) under an atmosphere of argon. The reaction mixture was allowed to warm to room temperature over 2 h and then stirred for a further 93 h. Acetic anhydride (10 ml) and pyridine (3 ml) were added, and the mixture stirred for a further 5 h. Concentrated HCl (20 ml)

was added, and the solution heated at 80°C for 6 h. Methylene dichloride (60 ml) was added to the cooled solution, followed by water (50 ml). After filtration through Celite, the filtrate was washed with water (2x50 ml), saturated aqueous $NaHCO_3$ (2x25 ml) and water (2x25 ml). The dried ($MgSO_4$) organic layer was reduced to 20 ml. Addition of methanol (50 ml) and filtration of the precipitate gave 4-acetoxy-3-(3'-nitrophenyl)-coumarin 34 (2.19 g, 83%) which crystallized as needles (ethanol-methylene dichloride), m.p. 188-189°C, ν_{max} (KBr) 1780, 1715, 1620, and 1538 cm^{-1}; λ_{max} ($CHCl_3$) 320(12804) and 281(18396) nm; δ ($CDCl_3$) 8.20-7.00 (8H, m, Ar) and 2.20 (3H, s, $COCH_3$); m/z 325 (M^+, 5), 283(100), 266(17), 236(11), 121(64), and 43(17) (Found: C, 62.96; H, 3.18; N, 4.42. $C_{17}H_{11}NO_6$ requires C, 62.79; H, 3.38; N, 4.30%).

Arylation of 4-Hydroxy-7-methoxycoumarin 28

a) With $Ph_3Bi(OAc)_2$ 21 : A mixture of 28 (0.10 g), 21 (0.247 g) in anhydrous methylene dichloride (10 ml) was stirred under reflux in the dark under an atmosphere of argon for 43 h. Work-up and preparative t.l.c. (eluant: $CHCl_3$-MeOH-H_2O 80:1:0.1) afforded 4-hydroxy-7-methoxy-3-phenylcoumarin 29 (0.114 g, 82%) which crystallized as plates (benzene-methanol), m.p. 203-204°C, lit.[22] 204°C, and 28 (0.005 g, 5%).

b) With $p\text{-}Tol_3Bi(OAc)_2$ 30 : A reaction as above performed with 28 (0.077 g), 30 (0.35 g) stirred under reflux for 45 h gave after work-up 4-hydroxy-7-methoxy-3-p-tolylcoumarin 32 (0.091 g, 80%) which crystallized as needles (benzene), m.p. 222°C, ν_{max} (KBr) 1656 and 1605 cm^{-1}; λ_{max} ($CHCl_3$) 317(22990) and 243 (8560) nm; δ_H (d_6-acetone + d_6-DMSO, 270 MHz) 9.88 (1H, br.s., -OH), 7.88 (1H, d, J 8.80 Hz, 5-H), 7.33 (2H, d, J 8.42 Hz, 3'-H, 5'-H), 7.26 (2H, d, J 7.70 Hz, 2'-H, 6'-H), 6.86 (1H, dd, J 8.80 Hz and 2.20 Hz, 6-H), 6.80 (1H, d, J 2.20 Hz, 8-H), 3.88 (3H, s, OCH_3), and 2.38 (3H, s, CH_3); δ_C ($CDCl_3$ + d_6-DMSO, 67.8 MHz) 163.51 (s, C-2), 162.75 (s, C-7), 160.87 (s, C-9), 154.41 (s, C-4), 137.38 (s, C-1'), 130.94 (d, C-2', C-6'), 129.26 (d, C-3', C-5'), 128.60 (s, C-4'), 125.00 (d, C-5), 111.74 (d, C-6), 109.70 (s, C-10), 103.65 (s, C-3), 100.13 (d, C-8), 55.68 (q, OCH_3), 21.26 (q, $-CH_3$); m/z 282 (M^+, 100), 151(96), and 132(83) (Found: C, 71.82; H, 5.17. $C_{17}H_{14}O_4$ requires C, 72.25; H, 4.96%), and 28 (0.008 g, 7%).

Preparation of 4-Acetoxy-3-(3'-acetoxyphenyl)coumarin 36

A suspension of 34 (0.10 g), and tin(II)chloride dihydrate (0.21 g) in concentrated HCl (2 ml) was vigorously stirred for 12 h at 80°C. After ice-cooling, the suspension was treated with a solution of sodium nitrite (0.022 g) in water (1.4 ml) added dropwise over 1 h in such a manner that the reaction temperature was maintained between 4-5°C. After stirring for a further 1 h at 0°C, water (10 ml) was added, and the reaction mixture heated in an oil bath at 90°C for 4 h. After cooling, the reaction mixture was extracted three times with a mixture of THF (8 ml) and methylene dichloride (10 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent distilled off. The oily residue was immediately dissolved in a mixture of pyridine (0.25 ml), acetic anhydride (1 ml), and methylene dichloride (2 ml), and stirred at room temperature for 4 h. The reaction mixture was washed with water (10 ml), dilute aqueous HCl (20%, 10 ml) and water (2x10 ml). Distillation of the solvent and preparative t.l.c. (eluant: chloroform-hexane 10:1) afforded 4-acetoxy-3-(3'-chlorophenyl)-coumarin 35 (0.026 g, 27%) which crystallized as needles (ethanol), m.p. 165-166°C, ν_{max} ($CHCl_3$) 1790, 1733, 1637, and 1617 cm^{-1}; λ_{max} ($CHCl_3$) 320(12902) and 281(14482) nm; δ ($CDCl_3$) 8.20-7.00 (8H, m, Ar) and 2.20 (3H, s, $CO\text{-}CH_3$); m/z 314 (M^+, 4), 272(100), 152(52), 121(66), and 43(36) (Found: C, 64.83; H, 3.45; Cl, 11.27. $C_{17}H_{11}ClO_4$ requires C, 64.89; H, 3.50; Cl, 11.27%), and 4-acetoxy-3-(3'-acetoxyphenyl)-coumarin 36 (0.063 g, 61%) which crystallized as needles (ethanol-methylene dichloride), m.p. 168-170°C, ν_{max} ($CHCl_3$) 1768, 1736, 1635, and 1610 cm^{-1}; λ_{max} ($CHCl_3$) 320(12887) and 287(13921) nm; δ ($CDCl_3$) 7.80-7.00 (8H, m, Ar), 2.33 (3H, s, $COCH_3$), and 2.18 (3H, s, $COCH_3$); m/z 338 (M^+, 2), 296(42), 254(100), 134(40), 121(77), and 43(37) (Found: C, 67.30; H, 4.18. $C_{19}H_{14}O_6$ requires C, 67.47; H, 4.14%).

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References

1. P.M. Dewick, in "The Flavonoids : Advances in Research", J.B. Harborne and T.J. Mabry Eds., Chapman and Hall, London, 1982, Isoflavonoids, p. 535.
2. D.R. Perrin and W. Bottomley, J. Am. Chem. Soc., 1962, 84, 1919.
3. a) S. Antus, A. Gottsegen, and M. Nogradi, Synthesis, 1981, 574. b) A. Robertson, C.W. Suckling, and W.B. Whalley, J. Chem. Soc., 1949, 1571. c) S.K. Aggarwal, S.K. Grover, and T.R. Seshadri, Indian J. Chem., 1969, 7, 1059. d) R. Gandhidasan, S. Neelakanten, and P.V. Raman, Synthesis, 1982, 1110. e) A.C. Jain and A. Mehta, J. Chem. Soc., Perkin Trans. I, 1986, 215. f) B.S. Kirkiacharian, J. Chem. Soc., Chem. Comm., 1975, 162.

4. a) A.H. Gilbert, A. McCookin, and A. Robertson, J. Chem. Soc., 1957, 3740. b) P. Vercier, D. Molho, and C. Mentzer, Bull. Soc. Chim. Fr., 1950, 1248. c) M. Geoghegan, W.I. O'Sullivan, and E.M. Philbin, Tetrahedron, 1966, 22, 3209. d) A.C. Jain, V.K. Rohatgi, and T.R. Seshadri, Tetrahedron, 1967, 23, 2499. e) V. Szabo, J. Borda, and E. Theisz, Acta Chim. Acad. Sci. Hung., 1980, 103, 271. f) K.N. Sawhney and K.B.L. Mathur, Indian J. Chem., Sect. B, 1976, 14B, 518.
5. R.F. Heck, J. Am. Chem. Soc., 1968, 90, 5535; R. Saito, T. Izumi, and A. Kasahara, Bull. Chem. Soc. Jpn., 1973, 46, 1776.
6. D.J. Ackland and J.T. Pinhey, J. Chem. Soc., Perkin Trans. I, 1987, 2689 and references therein.
7. D.H.R. Barton and J.P. Finet, Pure and Appl. Chem., 1987, 59, 937 and references therein.
8. D.H.R. Barton, J.P. Finet, C. Giannotti, F. Halley, and P. Krausz, in preparation; F. Halley, Ph.D. Thesis, University of Paris-Sud, Orsay, France, 1986.
9. A.P. Krapcho and A.J. Lovey, Tetrahedron Lett., 1973, 957.
10. D.H.R. Barton, J.C. Blazejewski, B. Charpiot, J.P. Finet, W.B. Motherwell, M.T.B. Papoula, and S.P. Stanforth, J. Chem. Soc., Perkin Trans. I, 1985, 2667.
11. A. Schmuck, J. Buschmann, J. Fuchs, and K. Seppelt, Angew. Chem., Intnl. Ed., 1987, 26, 1180.
12. C. Pichon, Ph.D. Thesis, University of Paris-Sud, Orsay, 1985.
13. D.H.R. Barton, J.P. Finet, J. Khamsi, and C. Pichon, Tetrahedron Lett., 1986, 27, 3619. See also: S. David and A. Thieffry, J. Org. Chem., 1983, 48, 441; V.A. Dodonov, A.G. Gushchin, and T.G. Brilkina, Zh. Obshch. Khim., 1984, 54, 2157, Chem. Abst., 1985, 102, 45543v.
14. D.H.R. Barton, N.Y. Bhatnagar, J.P. Finet, and W.B. Motherwell, Tetrahedron, 1986, 42, 3111.
15. R.P. Kopinski, J.T. Pinhey, and B.A. Rowe, Aust. J. Chem., 1984, 37, 1245, and references therein.
16. R.G. Goel and H.S. Prasad, Canad. J. Chem., 1970, 48, 2488.
17. D. Vorländer, Ber. Dtsch. Chem. Ges., 1925, B58, 1893.
18. J.V. Supniewski and R. Adams, J. Am. Chem. Soc., 1926, 48, 507.
19. A.O. Fitton and G.R. Ramage, J. Chem. Soc., 1962, 4870.
20. J.D. Loudon and R.K. Razdan, J. Chem. Soc., 1954, 4299.
21. a) M. Davis, M. Pettett, D.B. Scanlon, and V. Ferrito, Aust. J. Chem., 1977, 30, 2289. b) T.R. Kasturi, K.M. Damodaran, G. Subrahmanyan, P. Brown, and G.R. Pettit, J. Chem. Soc., Chem. Comm., 1968, 794.
22. J. Boyd, A. Robertson, and W.B. Whalley, J. Chem. Soc., 1948, 174.
23. R. Hüttel, K. Franke, H. Martin, and J. Riedl, Chem. Ber., 1960, 93, 1433.
24. M. Inoue, Sci. Rep., Tohoku Univ., Ser. 1, 1961, 45, 63; Chem. Abst., 1963, 58, 5619b.
25. B. Van Zanten and W.T. Nauta, Arzneimittel Forsch., 1964, 14, 29.