Synthesis of 3-Benzoyl-3,4-dihydro-2*H*- and 3,4-Dihydro-2,2-disubstituted-benzopyrans *via* Alkynyl Grignard Reagents

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The versatility of the new route to a substituted chromane *via* a lithiated allene recently described by us [1] is reported. The relatively more stable alkynols 2-4 were readily identified and thus provide evidence for the formation of vinyl acetylene carbinol as an intermediate in the new route. Accordingly, phenylacetylene magnesium bromide [2] reacted with suitable aldehyde or ketone to give the alkynols 2-4 which condensed further with the same or different aldehyde or ketone to give 3-benzoyl heteroring-substituted chromanes 5-17.

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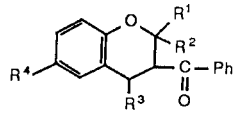
As a follow-up of our recent report on a new route to chromanes [1] attention has been directed at establishing the general synthetic possibilities of the route by supportive synthesis of chromanes containing a wide variety of substituents incorporated as R^1, R^2, R^3 and R^4 in the molecule.



5-17

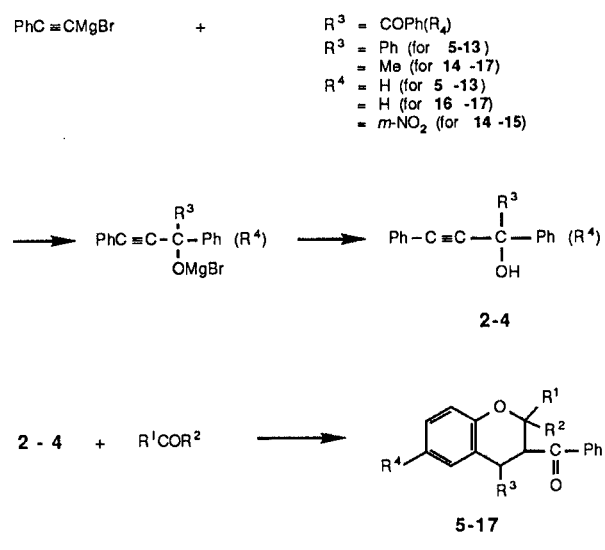
We have also confirmed the mechanism proposed for the new route by starting each synthesis with a stable and identifiable acetylenecarbinol. The oxygens of the hydroxyl groups of the carbinols **2-4** *via* the new route appeared in the chromanes **5-17** as the 3-benzoyl oxygen atoms. As described for the allene, the heteroatom was incorporated at the last stage of each synthesis.

The starting material was phenylacetylene obtained commercially and purified by standard methods. This was converted to phenylacetylene magnesium bromide **2**. The Grignard reagent after treatment with one equivalent of the appropiate carbonyl compound gave quantitative yields of the carbinols **2-4** (Scheme 1).

The acetylenic carbinols **2-4** further reacted with appropiate ketone or aldehyde to give the chromanes **5-17**. The selectivity characteristic of the reaction route is very high, since the substituents, can be varied. The type of the C-3 substituent however, depends on the nature of the allene or acetylene used as the starting material.

The chromanes and their precursors were all characterised by spectroscopic and elemental analysis. The ir spectra of ethynylcarbinols **2-4** were all characterised by the expected hydroxyl group absorptions ranging from 3460 to 3550 cm^{-1}, for the ethynic C-C bond at 2220 cm^{-1} and for the benzene ring at 1600 cm^{-1}. In addition compound **3** showed an absorption for the nitro group at 1500 and 1380 cm^{-1} and **3** and **4** for the methyl substituent at 1350

Scheme 1. Reaction Sequence to Chromanes **5-17**

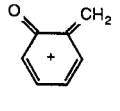


R^1 = H (for **5, 7, 10, 11, 12, 14, 15** and **17**)
= Me (for **6, 8** and **16**)
= Ph (for **9**)
R^2 = Me (for **5** and **6**)
= $CH(CH_3)_2$ (for **7**)
= $-CH=CH_2$ (for **8**)
= Ph (for **9**)
= *p*-OMePh (for **10**)
= *p*-NO_2Ph (for **11**)
= furyl (for **12, 15** and **17**)
= $-CH=CHPh$ (for **14**)
= *m*-NO_2Ph (for **16**)
R^1 + R^2 = cyclohexyl (for **13**)

cm^{-1}. The three carbinols were free from carbonyl conterminants since there was no carbonyl absorption in their ir spectra and purity was further ascertained by tlc.

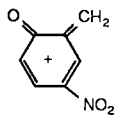
As expected, the ir spectra of chromanes **5-17** where characterised by the C-3 benzoyl carbonyl absorption at between 1700 and 1650 cm^{-1}. The absorption at between 1100 and 1030 cm^{-1} was assigned to the pyranyl C-O-C ether bond. The benzene ring absorption at around 1600 cm^{-1} was as expected prominent in each spectrum. In addition, chromanes **11, 16** and **17** showed absorptions for the nitro group at about 1550 cm^{-1} and 1380 cm^{-1}. The ^1H nmr spectra of **5-17** were in agreement with the structures

assigned and revealed an in-depth detail of features of each compound. Each spectrum gave the number of protons expected for the aromatic rings present in the molecule. Nitro groups in the benzene rings of **11**, **16** and **17** however caused lower downfield appearance of signals at between δ 8.30-8.79 in **11**, between 8.10 and 8.40 as a multiplet in **16**, and between 7.40 and 8.50 as another multiplet in **17**. The absorptions ranges described, however, include the non-substituted aromatics which absorbed slightly up field. A singlet at 0.95 for three hydrogens was prominent in the spectrum of **5**, and at 1.0, for six hydrogens of C-2 *gem*-dimethyl substituents in **6**. In the spectrum of **7**, a singlet appeared at δ 1.10 for the C-2 isopropyl methyl hydrogen, at 1.30 for H-2 and H-3 and at a lower field, δ 5.55 for H-4 due to the deshielding effect of the two C-4 phenyl residues. The C-2 methyl hydrogens absorbed as a singlet in 8 at δ 1.35, as a doublet for terminal C-2 vinyl hydrogens at δ 5.40, for the C-2 vinyl methine hydrogen at δ 5.55, and for the H-3 and H-4 as a singlet and doublet at δ 2.44 and 2.90 respectively. For compound **9**, H-3 and H-4 each appeared as a doublet at 3.16 and 5.40 respectively. The H-2 of 10 absorbed as doublet at δ 3.30, H-3 as a doublet at 2.40 and H-4 at δ 5.55. The methoxy methyl of C-2 p-anisyl residue, absorbed, as expected as a singlet much up field at δ 1.32. In **11**, both H-2 and H-3 absorbed at δ 2.70, and H-4, unusually much downfield at 7.70. The absorption pattern of H-2, H-3 and H-4 in compounds **12** and **13** were similar to that in **10** *viz* at δ 1.86, 1.25 and 2.60 respectively, each signal appearing as a broad singlet. Compounds **14** and **15** also had spectra containing comparable absorptions. The C-4 methylhydrogens of **14** absorbed at δ 0.8, and for compound **15** the signal appeared at δ 1.13. In the spectrum of **14** the two C-2 cinnamyl methine hydrogens appeared at δ 6.50. Other hydrogens in **14**, H-2, H-3 and H-4 absorbed at δ 2.20, 1.20 and 1.20 respectively. For **15**, the H-2, H-3 and H-4 signals occurred at δ 2.80, 2.40 and 2.30 respectively. The C-2 and C-4 methyl hydrogens of **16** on the other hand all absorbed at δ 1.30. The other expected absorptions, H-3 and H-4 absorbed at δ 1.55. The spectrum of **17**, the last compound synthesised contained a singlet for the C-4 methyl protons at δ 2.0. The H-2, H-3 and H-4 signals appeared at δ 3.50, 2.80 and 2.80 respectively. In all the ^{1}H nmr spectra examined, the chemical shifts and splitting patterns of signals were consistent with the structures assigned to chromans **5-17**.



C_7H_5O (m/e 105)

18



$C_7H_4NO_3$ (m/e 150)

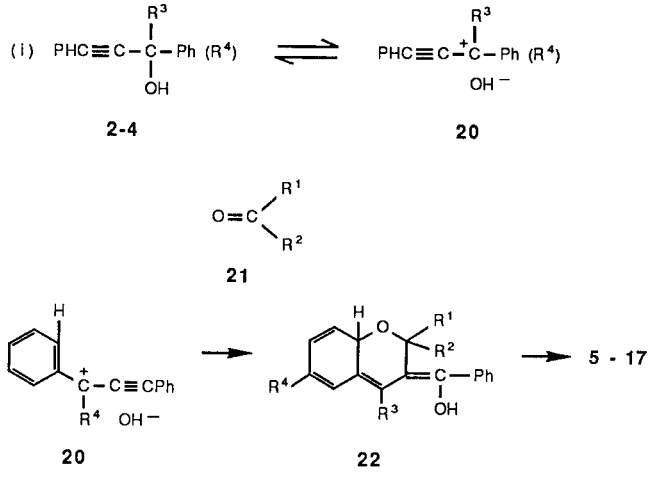
19

The mass spectra of the chromans either showed very weak or no mother ion peaks as expected for aromatic ethers due to the McLafferty rearrangement [3].

Only four of the chromans showed very weak molecular ions: compounds **7**, **12**, **15** and **16**. Other molecular ions were undetectable. All the spectra however, contained ion peaks characteristic of any chromanes that may be synthesised by the new route *e.g.* ion **18**, m/e 105 in **7-11** and **15-16**, and 19 m/e 150 in **12**. Further confirmation of structures of chromanes **5-17** was achieved through elemental analysis.

The mechanism of the transformation of the organoacetylenes *via* the alkynyl carbinols **2-4** to the chromanes **5-17** is similar to the one outlined for transforming an allene to a chromane [1]. The tertiary alkynyl carbinols **2-4** dissociate reversibly to the carbocation **20** trapped alongside the hydroxy-ion (Scheme 2). The keto or aldehydic carbonyl compound **21** reacts with **20** producing the tetraenol **22** which aromatised to the 3-benzoylchromane **5-17**. Here, the corresponding C-3 enol is the less stable isomer; the keto isomer being stabilised by conjugation with the adjacent benzene ring. In all the reactions here, that was the observation.

Scheme 2. Mechanism of Transformations of Carbinols **2 - 4** to Chromanes **5 - 17**



EXPERIMENTAL

Infrared spectra were run in Nujol Mulls or as a thin oil film on sodium chloride discs with a Perkin Elmer 257 spectrophotometer. The ^{1}H nmr spectra were determined with a 60 MHz instrument for solutions in deuteriochloroform with trimethylsilane as the internal standard. Micro-analysis was done with a Perkin Elmer 200 instrument.

1,1,3-Triphenyl-prop-2-yn-1-ol (**2**).

The usual standard procedure, [2] was followed. Magnesium turnings (6.0 g, 0.25 mole), and a crystal of iodine in anhydrous ether (50 ml) was treated with bromoethane (19.0 ml) followed by a dropwise addition of purified phenylacetylene (25.5 g, 7 ml, 0.25 mole) in anhydrous ether (30 ml). When all the magnesium turnings had reacted, the mixture was

refluxed for further 2 hours. It was then cooled to room temperature. Benzophenone (45.5 g, 0.25 mole) in ether (50 ml) was added while stirring continued. After the addition, stirring continued for a further 2 hours. The mixture was heated under reflux for 1 hour, cooled, (0°) and the Grignard complex decomposed by a slow addition of a saturated solution of ammonium chloride (55.0 g). Workup afforded an oil which crystallised from petroleum ether (60-80°/ether) as a yellow solid **2**, 32 g (45%) mp 78-80°; ir: ν 3550 (OH), 2220 (−C≡C), 1600 (benzene) cm^{-1}.

2-Methyl-4-phenyl-3-benzoylchromane (**5**).

1,1,3-Triphenyl-prop-2-yn-1-ol (8.52 g, 0.03 mole) in THF (50 ml) at 0°, was treated with ethanal (1.7 ml, 0.03 mole) in THF (50 ml) with stirring. Further stirring at 0° was continued for 2.5 hours. The cooling bath was removed and stirring continued for 24 hours. Water was added and the mixture extracted with diethyl ether (4 x 50 ml). The combined orgnic solution was washed twice with water (50 ml) and dried over anhydrous magnesium sulphate. Solvent was removed with a rotatory evaporator and the residue crystallised from cold methanol giving chromane **5** as a dark brown viscous oil; ir: ν 1660 (C=O), 1600 (benzene ring) and 1070 (C−O−C−) cm^{-1}; nmr: δ 0.95 (s, 3H, OCH_3), 3.30 (d, 1H, PhCOCH), 4.0 (d, 1H, MeCH), 5.50 (d, 1H, PhCHPh), and 6.70-8.0 (m, 14H, ArH).

Anal. Calcd. for $C_{25}H_{20}O_2$: C, 84.15; H, 6.10. Found: C, 83.90; H, 6.25.

2,2-Dimethyl-4-phenyl-3-benzoylchromane (**6**).

This was prepared as described for **5** from 1,1,3-triphenyl-prop-2-yn-1-ol (8.52 g, 0.03 mole) in THF (50 ml) and acetone (2.2 ml, 0.03 mole) in THF (20 ml). The reaction mixture was stirred for 72 hours. After the usual workup the product, a yellow oil obtained, was titurated several times with ice-cold methanol to give chromane **6**, 4 g (14%); ir: ν 1660 (C=O), 1600 (benzene ring), and 1071 (C−O−C) cm^{-1}; ^1H nmr δ 1.0 (s, 6H, $C-(CH_3)_2$), 2.10 (d, 1H, PhCOCH), 5.52 (d, 1H, PhCHPh) and 6.50-7.32 (m, 14H, ArH); ms: 270 (49), 269 (51), 182 (54), 105 (100).

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.21; H, 6.49. Found: C, 84.01; H, 6.52.

2-Isopropyl-4-phenyl-3-benzoylchromane (**7**).

This was prepared from 1,1,3-triphenyl-prop-2-yn-1-ol **2** (8.52 g, 0.03 mole) in THF (50 ml) and isobutyl aldehyde (2.7 ml, 0.03 mole) in THF (30 ml). After the usual workup, the product, after recrystallisation from methanol, afforded chromane **7** as yellow crystals, 6.0 g (56%) mp 320-332°; ir: ν 1650, (C=O), 1600 (aromatic), 1070 (C−O−C) cm^{-1}; ^1H nmr: δ 1.10 (s, 6H, $C(CH_3)_2$, 1.30 (br, 2H, $CHMe_2$ and PhCOCH), 5.5 (d, 1H, PhCHPh), 5.70-6.60 (m, 14H, ArH); ms: M^+ 356 (0.1), 284 (50.7), 283 (53), 183 (56.4), 180 (94), 105 (100), 77 (85.2).

Anal. Calcd. for $C_{25}H_{24}O_2$: C, 84.27; H, 6.74. Found: C, 83.86; H, 6.80.

2-Methyl-2-vinyl-4-phenyl-3-benzoylchromane (**8**).

1,1,3-Triphenyl-prop-2-yn-1-ol, 2 (8.52 g, 0.03 mole) in THF (50 ml) was stirred at 0° with methyl vinyl ketone (2.2 ml, 0.03 mole) in THF (30 ml). After the usual reaction and workup, the product crystallised from methanol to give a pink powder 6.4 g (60%) mp 185-187°; ir: ν 1650 (C=O), 1600 (benzene ring), and 1060 (C−O−C) cm^{-1}; ^1H nmr: δ 1.55 (s, 3H, $C-CH_3$), 2.4 (s, 1H, PhCOCH), 2.90 (s, C-2 vinyl methine H), 5.40 (s, 2H, C-2 terminal vinyl hydrogens), 5.55 (d, 1H, PhCHPh), 5.70-6.60 (m, 14H, ArH); ms: 295.0 (0.8), 283 (8), 0.15 (44), 85 (44), 71 (58).

Anal. Calcd. for$C_{25}H_{22}O_2$: C, 84.75; H, 6.21. Found: C, 84.36; H, 6.35.

2,2,4-Triphenyl-3-benzoylchromane (**9**).

1,1,3-Triphenyl-prop-2-yn-1-ol, 2 (8.52 g, 0.03 mole) in THF (50 ml) was treated with benzophenone (5.46 g, 0.03 mole) in THF (40 ml). The reaction was carried out as described for **5**. After workup the product, crystallised from cold methanol to give **9** as a dark viscous oil 12.4 g (89%); ^1H ir: ν 1660 (C=O); 1600 (benzene ring), 1070 (C−O−C) cm^{-1}; nmr: δ 3.16 (d, 1H, PhCOCH), 5.40 (d, 1H, PhCHPh), 6.50-8.60 (m, 19H, ArH); ms: 40% 184 (57), 105 (100).

Anal. Calcd. for $C_{34}H_{26}O_2$: C, 87.55; H, 5.58. Found: C, 87.42; H, 5.32.

2-(*p*-Methoxyphenyl)-4-phenyl-3-benzoylchromane (**10**).

1,1,3-Triphenyl-prop-2-yn-1-ol, 2 (8.52 g, 0.03 mole) in THF (50 ml) was reacted as before, with *p*-methoxybenzaldehyde (4 ml, 0.03) in THF (50 ml) at 0°. Workup, after the usual reaction gave a product which crystallised from methanol to give a pink powder, 12.0 g (96%) mp 90-92°; ir: ν 1660 (C=O), 1600 (benzene ring) 1070 (−C−O−C) cm^{-1}; nmr: δ 1.32 (s, 3H, OCH_3), 2.40 (d, 1H, PhCOCH), (s, 1H, H-2), 3.30 (s, 1H, H-2), 5.55 (d, 1H, PhCHPh), 5.70-6.70 (m, 18H, ArH); ms: 284 (2), 182 (43), 105 (100), 77 (53).

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 82.86; H, 5.71. Found: C, 82.49; H, 5.85.

2-(*p*-Nitrophenyl)-4-phenyl-3-benzoylchromane (**11**).

This involved the usual slow, with stirring addition of *p*-nitrobenzaldehyde (4.53 g, 0.03 mole) in THF (10 ml) to 1,1,3-triphenyl-prop-2-yn-1-ol (8.52 g, 0.03 mole) in THF (50 ml). The reaction mixture was worked up as before, and the product recrystallised from petroleum ether (60-80°). This afforded chromane **11** as yellow crystals, 4.7 g (36%), mp 102-104°; ir: ν 1700 (C=O), 1600 (benzene ring), 1550 and 1382 (NO_2) and 1100 (C−O−C) cm^{-1}; nmr: δ 2.7 (m, 3H, H-2, H-2, H-3), 7.70 (m, 1H, PhCHPh), 8.30-8.79 (m, 18H, ArH); ms: 369 (0.1), 252 (41), 150 (100), 104 (76), 76 (53).

Anal. Calcd. for $C_{28}H_{21}NO_4$: C, 77.24; H, 4.83; N, 3.22. Found: C, 77.12; H, 4.75; N, 2.99.

2-Furyl-4-phenyl-3-benzoylchromane (**12**).

Reaction involved 1,1,3-triphenyl-prop-2-yn-1-ol **2** (8.52 g, 0.03 mole) and furfural (2.49 ml, 0.03 mole) in THF (30 ml). After the workup, the product crystallised from methanol to give chromane **12**, 7.3 g (67•) as red crystals, mp 53-55°; ir: ν 1660 (C=O), 1600 (benzene ring), 1070 (C−O−C); nmr: δ 1.25 (d, 1H, PhCOCH), 1.86 (s, 1H, H-2), 2.60 (s, 1H, PhCHPh), 6.50-7.92 (m, 17H, ArH); ms: M^+ 384 (2), 151 (46), 150 (71), 105 (100), 77 (91).

Anal. Calcd. for $C_{26}H_{20}O_3$: C, 82.11; H, 5.26. Found: C, 81.97; H, 5.45.

2,2-Cyclohexyl-4-phenyl-3-benzoylchromane (**13**).

The alkynol **2** (8.52 g, 0.03 mole) in THF (50 ml) at 0° was treated while stirring with cyclohexanone (3.12 ml, 0.03 mole) in THF (30 ml). Workup after reaction, afforded chromane **13** as yellow oil 5.9 g (52%) after titutration from methanol; ir (film): ν 1680 (C=O), 1600 (benzene ring), 1070 (C−O−C) cm^{-1}; nmr: δ 1.25-1.31 (m, 10H, C-2 cyclohexylprotons), 1.87 (d, 1H, PhCOCH), 5.20 (d, 1H, PhCHPh) and 6.70-8.30 (m, 14H, ArH).

Anal. Calcd. for $C_{27}H_{26}O_2$: C, 84.82; H, 6.81. Found: C, 84.61; H, 6.95.

2,4-Diphenylbut-3-yn-2-ol (**3**).

To the phenylacetylene magnesium bromide (as for **2**), acetophenone (30 ml, 0.25 mole) in dry ether (50 ml) was added very slowly and with stirring. The product after workup and tituration with petroleum ether (60-80°) afforded 2,4-diphenylbut-3-yn-2-ol **3** 28.9 g (52%); ir: ν 3500, (OH) 2220 (C≡C), 1600 (benzene) cm^{-1}.

2-Cinnamyl-4-methyl-3-benzoylchromane (**14**).

2,4-Diphenylbut-3-yn-2-ol 3 (6.69 g, 0.03 mole) in THF (50 ml) was treated as usual at 0° with cinnaldehyde (3.78 ml, 0.03 mole) in THF (30 ml). The product, after tituration with methanol afforded 8.0 g (75%) of a dark brown oil; ir: ν max 1680 (C=O), 1600 (benzene ring), 1100 (C−O−C) cm^{-1}; nmr: δ 0.8 (s, 3H, C-4 methly), 1.20 (s, 2H, H-3 + H-4), 2.60 (s, 1H, H-2), 6.50-8.30 (m, 22H, ArH), 9.85 (s, vinyl H); ms: (m/e relative intensity) 339 (49.3), 184 (53), 105 (100.0), 72 (79).

Anal. Calcd. for $C_{25}H_{22}O_2$: C, 84.75; H, 6.21. Found: C, 84.59; H, 6.49.

2-Furyl-4-methyl-3-benzoylchromane (**15**).

2,4-Diphenylbut-3-yn-2-ol, **3** (6.69 g, 0.03 mole) in THF (50 ml) was treated with furfural (2.49 ml, 0.03 mole) at 0°. The product after the usual reaction and workup afforded, after crystallisation from methanol, a pink powder of chromane **15** 9.1 g (95%), mp 60-62°; ir: ν 1660 (C=O), 1600 (benzene ring), 1030 (C−O−C) cm^{-1}; nmr: δ 1.3 (s, 3H, CH_3), 2.30 (s, 1H, PhCHPh), 2.40 (s, 1H, PhCOCH), 2.8 (s, 1H, H-2), 6.0-8.4 (m, 12H,

ArH); ms: M^+, 318 (0.4), 283 (42), 105 (100), 102 (71.0), 102 (77).

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.25; H, 5.66. Found: C, 79.60; H, 5.43.

2-(*m*-Nitrophenyl)-4-phenylbut-3-yn-2-ol (**4**).

Phenylacetylene magnesium bromide was prepared using the same quantities of reagents as used for **2**. To the Grignard reagent was added slowly, *m*-nitroacetophenone (41.25 g, 0.25 mole) in dry ether (50 ml). After the usual workup and tituration with petroleum ether the product, 2,4-diphenylbut-3-yn-2-ol **4** was obtained as a yellow oil 28.4 g (40%); ir: ν 3460 (OH), 2220 (C≡C), 1600 (benzene ring), 1500 and 1380 (NO_2) cm^{-1}.

2-Methyl-2-*m*-nitrophenyl-4-methyl-6-nitro-3-benzoyl chromane (**16**).

2-*m*-nitrophenyl-4-phenylbut-3-yn-2-ol, **4** (8.0 ml, 0.03 mole) in THF. (50 ml) was treated as described for chromane **5** at 0°, with *m*-nitroacetophenone (4.95 g; 0.03 mole) in THF (30 ml). After the usual workup, the product, after recrystallisation from petroleum ether (60-80°) afforded 5.2 g (40%) of chromane **16** as yellow crystals mp 72-74°, ir: ν 1680 (C=O); 1610 (benzene ring); 1110 (C−O−C) cm^{-1}; nmr: δ 1.55 (s, 3H, H-2 + H-3 + H-4); 8.10-8.40 (m, 13H, ArH); ms: M^+, 432 (0.1): 207 (24); 105 (100); 77 (36).

Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C, 66.67; H, 4.63; N, 6.48. Found: C, 66.89; H, 4.57; N, 6.19.

2-Furyl-4-methyl-6-nitro-3-benzoyl chromane (**17**).

The alkynol **4** (8.0 g, 0.03 mole) in THF (50 ml) was treated at 0° with furfural (2.49 ml, 0.03 mole) in THF (30 ml). After completion of reaction and the usual workup, the product, after crystallisation from methanol afforded chromane **17** as dark brown crystals 3.5 g (32%); mp 88-90°; ir: δ 2.0 (s, 3H, CH_3); 2.83 (s, 2H, H-3 + H-4); 3.5 (s, H-2); 6.60-7.30 (t, 3H, 2-furyl); 7.40-8.50 (m, 9H, benzene hydrogens); ms: 315 (0.4); 151 (98); 150 (100).

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.42; H, 4.68; N, 3.86. Found: C, 69.70; H, 4.45; N, 3.64.

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