Synthesis of 2,2,4-Triphenyl-3-propenoyl-3,4-dihydro-2*H*-benzopyran via a lithiated Allene

E. A. Adegoke,* T. A. Emokpae and H. Ephraim-Bassey

Chemistry Department, Faculty of Science, University of Lagos,
Lagos, Nigeria
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Synthetic routes to 2,2-disubstituted chromanes and their hetero-ring-unsaturated analogues are briefly reviewed. A variety of common alkylating agents has been involved in such routes. Here, however, the alkylating agent is the lithiated form of 4-tetrahydropyran-2-yloxybuta-1-2-diene V. This reacted with benzophenone to give XIV. The synthesis of chromane XIV is here reported for the first time. The route to XIV is also both new and may prove versatile to other hetero-ring-substituted chromanes.
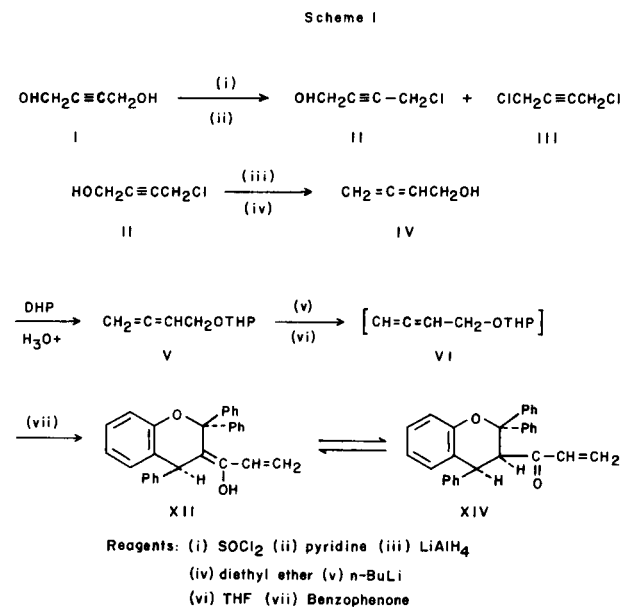
The renewed interest in the chromanes and chromenes is due to the importance of certain 2,2-disubstituted chromanes as vitamins, the stimulating photochromic behaviour of some chromenes, the ever-increasing number of natural products in which the ring system exists *e.g.* the flamingins [1] and their ready conversion to 2,2,4-trisubstituted chromenes, some of which have been patented as biologically active substances [2,3]. The allenyl group has also been found to be responsible for the bioactivity of many natural products [4,5,6]. Compound XIV in this report is a 2,2,4-triphenylchromane and therefore satisfies the structural requirements for the biological activity indicated above. The C-3 atom also carries a vinyloyl substituent convertible to an allenyl function. This may also induce bioactive properties characteristic of allenyl moiety.

XIV
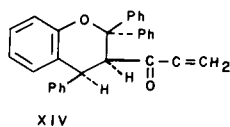
Karrer *et al* in 1938 synthesised the well known (±) α-tocopherol by a Friedel Crafts alkylation of trimethylquinol with phythyl bromide followed by cyclisation. Miller *et al*, however in 1965 used phythyl diphenyl phosphate for the synthesis. 2,2,4-Trimethyl-4-*p*-hydroxyphenylchromene, on the other hand, was obtained by reacting phenol with dimethyl-allyl methyl ketone. Pyrolysis induced elimination in the product thereby yielding 2,2,4-trimethylchrom-3-ene [7]. There are many other routes to the chromenes, all of which may be reduced to the chromanes. Wittig reaction between a salicylaldehyde and an alkyltriphenyl-phosphonium salt produced an adduct which afforded *via* a [1-7] sigmatropic shift a quinoneallide which thermally cyclised to the chromene. A high-yield variation of this route involved the addition of the phenolate anion of salicylaldehyde to a vinyl-phosphonium salt. Propargyl ethers (from the phenolate anion and propargyl halide) on the other hand, underwent Claisen re-arrangement to a 2-alkenylphenol which also through a

[1-5] sigmatropic shift to a quinoaneallide thermally cyclised to the chromene [8]. Other chromene-producing reactions with quinoneallides as intermediates include reactions between 3,3-dimethylallyl-triphenylphosphorane and *o*- or *p*-benzoquinones [9], benzyne and αβ-unsaturated aldehydes [10] and the thermal 1,4-elimination of water from *o*-hydroxyphenylallyl alcohols formed between salicylaldehyde or *o*-hydroxyacetophenone and a vinylmagnesium halide [11]. Epoxidation, followed by base-promoted elimination to a substituted *o*-hydroxycinnamyl alcohol, on pyrolysis also afforded 2,2-dialkyl or diarylchromenes. On the other hand, a benzylic alcohol is the intermediate in chromene-forming reactions involving resorcinols and αβ-unsaturated aldehydes [12].

The starting material for the present synthesis was but-2-yn-1,4-diol I obtained commercially and purified by standard procedure before use (Scheme 1).

Scheme I

Reagents: (i) SOCl₂ (ii) pyridine (iii) LiAlH₄
(iv) diethyl ether (v) n-BuLi
(vi) THF (vii) Benzophenone

Chlorination of the diol in pyridine was achieved by treatment with thionyl chloride [13,14]. The predominant product was the monochloroalkyne II at the low tempera-

ture of the reaction. This was, however, contaminated by the dichloroalkyne III separated from the former by distillation at reduced pressure. 4-Chlorobut-2-yn-1-ol, compound II, a liquid, showed all the expected characteristic ir absorptions, at 3650, 2250 and 200 cm⁻¹ for the hydroxyl group, alkynyl carbon-carbon bond and carbon-chlorine bond stretchings respectively. A fairly good yield of allene IV, buta-2,3-diene-1-ol was obtained by lithium aluminium hydride reductive elimination of chloride from II [15]. The yield was, however, a little lower than anticipated due to loss arising from high volatility of product during distillation. The expected hydroxyl and allenyl ir absorptions at 3600 and 1960 cm⁻¹ respectively were observed. In the ¹H nmr spectrum of compound IV the three allenic protons absorbed at between δ 4.3 and 5.3. The hydroxyl singlet signal at δ 2.68 disappeared on deuteration.

Lithiation of allene IV was preceded by pyranylation [16,17] to protect the hydroxyl group since any of the allenyl terminal hydrogens and the hydroxy group hydrogen was prone to metallation. The allene was unaffected by the protection procedure. The allenyl band at 1965 cm⁻¹ and the characteristic pyranyl ether bands were present in the ir spectrum and no hydroxyl or acetylenic absorption was observed. A multiplet proton absorption at δ 5.12 for the pyranyl ether group in the ¹H nmr spectrum was also significant.

Pilot experiments involving lithiation of the pyranyl ether V followed by alkylation with 1,3-dibromopropane or 1,3-bromochloropropane using alkylation procedures reported by Michelot [18] and Gore et al [19] were unsuccessful in our own trials, even in the presence of a variety of catalysts including hexamethylphosphoric triamide. However, alkylation was effected in the presence of an excess amount of benzophenone. This afforded 2,2,4-triphenyl-3-propenoyl-3,4-dihydro-2H-benzopyran XIV. The ir spectrum of compound XIV showed no pyranyl ether bands but indicated the presence of α,β-unsaturated carbonyl band and aromatic rings. The ¹H nmr spectrum contained two terminal olefinic hydrogens as signals at δ 2.9 (J_{AB} = 20 Hz) and signal for two vicinal olefinic hydrogens at δ 5.8 (J_{AX} = 20 Hz, J_{BX} = 15 Hz). It also contained signal for nineteen aromatic hydrogens at between δ 7.0 and 8.0. This is consistent with the presence of at least three aromatic rings in compound XIV. The λ max absorptions at 227 and 254 nm for the compound provided additional evidence. A molecular formula of $C_{30}H_{24}O_2$ obtained from elemental analysis and the spectral data just given are in agreement with the assigned structure. From previous work [20,21], one of the phenyl groups at C-2 must be equatorial and the other axial. A $J_{2,4}$ value of about 2 Hz obtained for similar compounds suggests that the bulky C-4 phenyl group must also be equatorial and its

hydrogen axial. Similarly, the C-3 vinyloyl substituent will be equatorial and its hydrogen axial.

The transformation of compound V to the benzopyran XIV was initiated by formation of the carbanion VI via lithiation (Scheme 2).

Scheme 2

(i) n-BuLi   (ii) Benzophenone.
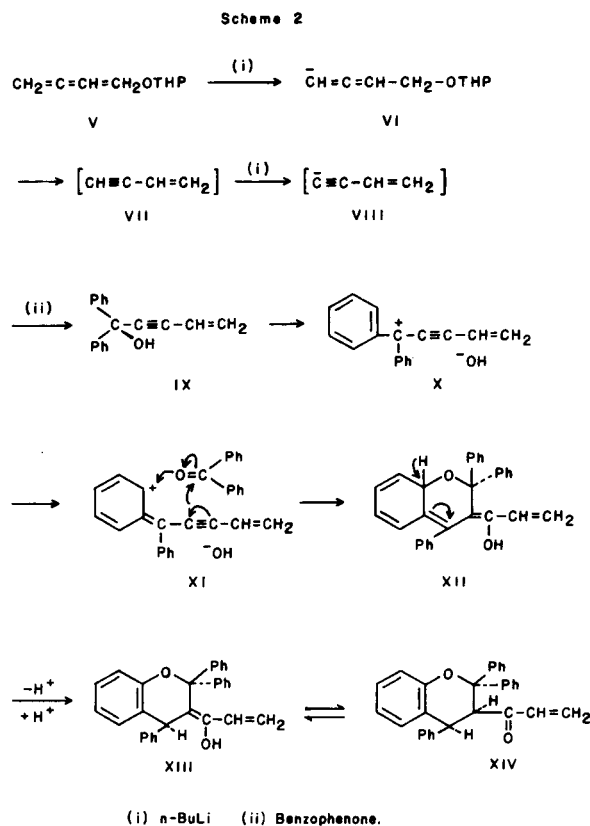
Structure VI acquired stability by ejecting the 2-tetrahydropyranoxy residue forming a rearranged product, vinylacetylene VII. Further lithiation of VII yielded the carbanion VIII which was immediately attacked by the electrophilic carbonyl carbon of one benzophenone molecule. The attack, followed by protonation resulted in structure IX. The carbonium ion X from the ionisation of alcohol IX rearranged to an alkynyl carbocation XI. The acetylenic carbon nearer to the charged ring in structure XI was then attacked by the electrophilic carbonyl carbon of a second benzophenone molecule resulting in the formation of the unstable bicyclic intermediate XII. The non-hetero ring of XII aromatised yielding the enol XIII which ketolised to the $\alpha\beta$-unsaturated compound XIV.

One important difference between this report and the previous ones [7,8,9,10,11,12] is that all the former in vitro synthetic reactions to chromanes and chromenes involved starting materials containing the atom which appeared in the final product as the hetero atom. Thus, the oxygen of the hydroxyl group in the starting materials such as

phenols, phenolic aldehydes or hydroxyketones or the oxygen in quinones, furans, *etc*, appeared as the hetero atom in the hetero ring of the chromane or chromene. The only exception as far as we know is the reaction between benzyne and $\alpha\beta$-unsaturated aldehydes [10]. Correspondingly, all natural 2,2-dialkylchromanes and chromenes are believed to originate *in vivo* from the alkylation of a phenol or a suitable precursor with an alkyl or allyl pyrophosphate [5] followed by cyclisation. In the *in vitro* reaction described here (Scheme 2), the hetero atom is incorporated at the tail end of the synthesis, XI → XII. Unfortunately, little biosynthetic work has been carried out in this field and so the hypotheses just outlined need the support of *in vivo* experiments. However, work is at present in progress in our laboratory to prepare many hetero-ring-substituted chromanes *via* the novel route just reported.

EXPERIMENTAL

Infrared spectra were run in carbon tetrachloride with a Perkin-Elmer 257 spectrophotometer. Ultraviolet spectrum was determined with Pye-Unicam Sp 1800 spectrophotometer. Nuclear magnetic resonance spectra were determined with Varian PHX 60, JOEL FX 200 and FX 90 for solutions in deuteriochloroform with trimethylsilane as internal standard. Microanalysis was done with a Perkin-Elmer 240 instrument.

4-Chlorobut-2-yn-1-ol (11).

But-2-yn-1,4-diol (288 g, 3.0 moles) in a mixture of dry benzene (333 g, 380 ml) and dry pyridine (290 g, 3.7 moles) was heated with stirring under reflux. Redistilled thionyl chloride (463 g, 3.9 moles) was then added over a period of 6 hours at 10-20° in an ice bath. After the addition, the mixture was stirred for an additional hour, and left to stand overnight. It was then poured into water (100 ml). The organic layer was separated and the aqueous layer extracted with ether (4 x 250 cm³). The combined organic solution was washed twice with saturated aqueous sodium bicarbonate and once with water. The extract was dried (magnesium sulfate + sodium sulfate) and excess solvent was removed by distillation at ordinary pressure. Residual solvent was finally removed with rotary evaporator. The residue was distilled at reduced pressure using a short Vigreux column. This afforded 1,4-dichlorobut-2-yne (III) (124.5 g, 30%), bp 58° (12 mm Hz), lit 57° (12 mn Hg); ν max 700 (C-Cl) absence of strong band at 2260-2150 cm⁻¹ and 4-chlorobut-2-yn-1-ol (11) (92.0 g, 26%) bp 50.2° (0.5 mg Hg); ν max (carbon tetrachloride): 3650 (OH) 2250 (-C≡C-), 700 (C-Cl) cm⁻¹.

Anal. Calcd. for C₄H₅ClO: C, 45.93; H, 4.78; Cl, 33.97. Found: C, 45.72; H, 4.80; Cl, 33.81.

But-1,2-dien-1-ol (IV).

A solution of 4-chlorobut-2-yn-1-ol (55.0 g, 0.55 mole) in dry ether (150 ml), was added dropwise to a stirred solution of lithium aluminum hydride (30 g, 0.79 mole) in dry ether (800 ml) in a round bottomed flask equipped with a magnetic stirrer, a reflux condenser, a dropping funnel and calcium chloride drying tube. When the addition was complete the reaction was refluxed gently for 3 hours. The reaction flask was cooled in an ice bath and water (100 ml) was added dropwise. This was followed by an addition of dilute hydrochloric acid (700 ml, 1:1). The organic layer was separated, the aqueous layer extracted with ether (4 x 150 ml) and the combined extract was dried (magnesium sulfate). Ether was removed over a steam bath and the residue distilled at a reduced pressure using a short Vigreux column. This gave buta-1,2-dien-1-ol (20.5 g, 55%), bp 49-52° (20 mm Hg) lit 48-50° (20 mm Hg); λ max (carbon tetrachloride): 3334 (OH), 2950 (OH), 1960 (C=C=C), 843 (C=C=CH₂) cm⁻¹; ¹H nmr (deuteriochloroform): 1.80 (2H, m, C=C=CHC*H₂*), 2.63 (1H, s, Oh), 5.20

(1H, m, C=C=C*H*).

4-Tetrahydropyran-2-yloxybuta-1,2-diene (V).

A mixture of buta-1,2-dien-1-ol (12.80 g, 0.18 mole) and 2,3-dihydropyran (75.6 g, 0.9 mole) was stirred and cooled to 0°. Concentrated hydrochloric acid (0.1 ml) was added and stirring at 0° continued for 10 minutes. The reaction flask was removed from the ice bath and allowed to stand overnight. Ether (150 ml) was added. The solution was washed with saturated aqueous sodium bicarbonate and dried (magnesium sulfate/potassium carbonate). The solvent was removed with rotary evaporator. The residue was distilled at reduced pressure to give 4-tetrahydropyran-2-yloxybuta-1,2-diene (17.3 g, 6%), bp 58-62° (0.9 mm Hg); ν max (carbon tetrachloride): 1960 (C=C=C), 1200, 1120, 980, 940, 870 and 820 (ether bands) cm⁻¹; ¹H nmr (deuteriochloroform): 1.60 (s, C=C=CHC*H₂*O) 3.5-4.0 (m, CH(CH₂)₃C*H₂*) 4.70 (1H, m, C*H*(CH₂CH)₃CH₂) 5.5 (m, C=C=C*H*CH₂OTH).

Anal. Calcd. for C₉H₁₄O₂: C, 70.43; H, 9.10. Found: C, 69.94; H, 9.36.

2,2,4-Triphenyl-3-(prop-2-en-1-one)-5,6-benzopyran (XIV).

n-Butyllithium (0.007 mole) was added to a 1:1 THF/hexane (15 ml) in a 3-necked flask equipped with a stirrer and placed under nitrogen. The flask was cooled (-50°) and 4-tetrahydropyran-2-yloxybuta-1,2-diene (1.0 g, 0.007 mole) in dry THF (5 ml) was added. Stirring at -50° continued for 1 hour. Benzophenone (2.54 g, 0.014 mole) in dry THF (10 ml) was added. After another one hour of stirring, the reaction mixture was allowed to warm to room temperature and was then left overnight with stirring. Water (100 ml) was added. The organic layer was separated and the aqueous layer extracted with ether (2 x 50 ml). The organic layer and ether extracts were combined, washed with water (2 x 50 ml), and dried (magnesium sulfate). Solvent was removed at reduced pressure. The residue was redistilled at a much reduced pressure (0.30 mm Hg) to give a product (0.54 g), bp 185° (0.3 mm Hg); ν max (carbon tetrachloride): 3100 (w, Ar-H), 1665 (C=O), 1600 cm⁻¹ (Ar-C) absence of characteristic pyranyl ether bands; λ max (ethanol): 227 (ϵ 9870), 254 (ϵ 7873) nm;

¹H nmr (deuteriochloroform): δ (2.9   (C=C$\diagdown$ $\overset{H_B}{\underset{H_A}{\diagup}}$) $J_{AB} \simeq$ 20 Hz) δ 5.8

(1H, d, $H_X \diagdown$ C=C$\diagdown$ $\overset{H_B}{\underset{H_A}{\diagup}}$) $J_{Ax} \simeq$ 20 Hz, $J_{Bx} \simeq$ 15 Hz), 7.4 (19H, m, Ar*H*).

Anal. Calcd. for C₃₀H₂₄O₂: C, 86.54; H, 5.77. Found: C, 86.35; H, 5.91.

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