SHORT PAPER

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Sodium naphthalenide-induced conversion of 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran into 4-hydroxy-3-salicyloylxanthone†

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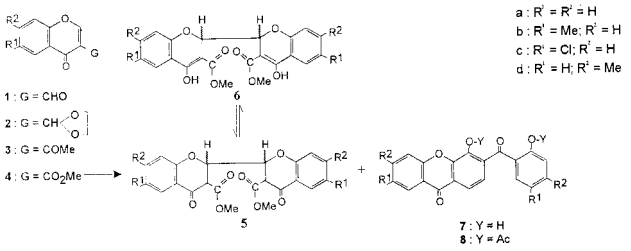
3- Methoxycarbonylchromenone **4** reacts with sodium naphthalenide to afford 4-hydroxy-3-salicyloylxanthone **7**, *via* the dimer **5**.

In recent years, the synthesis of xanthone derivatives has attracted special attention due to their many biological activities specially as antitumour agents[1] A small liophilic substituent at the C-5 position of xanthone-4-acetic acid enhances the dose potency as an antitumour agent.[2] The antibiotic bikaverin,[3,4] which contains benzo[b]xanthone skeleton, has a high vacuolation property and is a fungal metabolite. Recently, a number of glycosides linked at the 2-position to 4, 5, 8-trimethoxyxanthone have been isolated from ethanolic solution of rhizome of *A. Calamus*.[5] In view of the natural occurrence and useful range of biological activity associated with the xanthone moiety, various methods have been developed for their syntheses. Most syntheses have been carried out from benzene derivatives and a few from benzopyran-4-ones.[6]

We intended to couple 3-functionalised 4-oxo-4*H*-1-benzopyrans through their 2-positions. This coupled product could serve as a precursor for many oxygenerated polycyclic compounds. We have recently reported[7] that 3-formylchromenone **1** fails to produce the desired coupled product when treated with sodium naphthalenide or zinc. Product formation was rationalised by considering the initial addition of electron to the aldehyde function of **1** rather at C-2 of the chromenone moiety. Treatment acetal **2** of sodium naphthalenide produced the same mixture of products as was obtained from **1**. An earlier report[8] showed that reactions of nucleophiles either with **1** or with **2** produce the same products. Reaction of sodium naphthalenide with ketone **3** produced 2-salicyloylxanthone as was obtained from base-catalysed transformation of **3**.[9]

Hydrodimerisation of α, β-unsaturated esters[10] by SmI_2, cyclodimerisation of α, β-unsaturated esters to cyclopentanone derivatives by Yb[11] or by sodium naphthalenide[12] are known. We used 3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran **4** as the substrate.

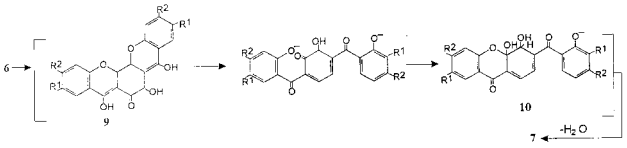


Scheme 1

The results of the reaction of **4** with sodium naphthalenide is reported herein.

The α,β-unsaturated ester **4** on treatment with sodium naphthalenide in the ratio 1:2.4 in dry tetrahydrofuran (THF) at 10–20°C under a nitrogen atmosphere produced the desired dimerised product **5** and a yellow compound **7** (Scheme 1). Compound **5** was found to be in the enol form **6** in chloroform, in which ^{1}H NMR spectrum was recorded. Of the two possible diastereomers of **6** only one was isolated except in the case of **4a** where both a *meso* and *dl* pair of **6a** was isolated. No **6d** was isolated from the reaction mixture of **4d**. Although the nature (*meso* or *dl*) of the diastereomers could not be assigned from their ^{1}H NMR spectra, the mode of further reaction helped in deciding which was which. It has been shown that *dl* pair undergoes further cyclisation,[13,14] which is obvious from steric considerations. Also the diastereomer which is susceptible towards further interaction between ester functionalities is the *dl* pair. So, the isolated dimer **6** can be presumed to be *meso* which remained unchanged when treated with NaOMe in MeOH.

The structure of the yellow compound **7** was established on the basis of ^{1}HNMR, IR and mass spectroscopy. The ^{1}H NMR spectrum of **7** showed the presence of two H-bonded OH groups which was also proved by formation of diacetate **8**. The two doublets with *ortho* coupling at around δ8.0 and δ7.7 and deshielding effect (by 0.4 ppm) on H-1 due to acetylation are particularly useful in supporting the structural assignment.



Scheme 2

The formation of **7** can be rationalised by considering an intramolecular acyloin-type condensation of the dimer **6** to form **9**. Dehydration of **10**, formed by the ring opening and ring closure of **9**, produced **7** (Scheme 2) in moderate yield. Compound **7c** was found to be admixed with **7a** in the ratio 4:1 (from ^{1}H NMR) which could not be separated. Compound **5c** showed no contamination of **5a**. From this observation it may be assumed that dechlorination takes place after cyclisation. The earlier reports of cyclodimerisation of α, β-unsaturated esters[11] or ketones[13] led to the formation of cyclopentanone or cyclopentanol derivatives, respectively except the reaction of benzylidene acetone with Yb[11] which produces a cyclohexanone derivative, although its formation could not be

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rationalised. But in this case, the formation of xanthone derivative **7** from **4** requires the formation of a six membered ring by cyclodimerisation of an α, β-unsaturated ester.

Experimental

All m.p. values are uncorrected. IR spectra were recorded on a Perkin Elmer 782 spectrometer in KRr. ^{1}H NMR spectra were recorded on a Bruker AM 300L spectrometer using Me_4Si as internal standard in $CDCl_3$, unless otherwise stated. Coupling constants are expressed in Hz and light petroleum refers to the fraction with b.p. 60–80°C.

*General procedure for the reaction of 3-methoxycarbonyl-4-oxo-4H-1-benzopyran **4** with sodium naphthalenide:* The ester **4**(5 mmol) dissolved in dry THF (20 ml) was injected into a solution of sodium naphthalenide [generated from naphthalene(1.54 g, 12 mmol) and sodium (330 mg, 14.4 mmol)] in dry THF (15 ml) under dry nitrogen at 10-20°C. The reaction mixture was stirred for 1 h at this temprature and poured into citric acid solution (10% 150ml). The organic matter was extracted with chloroform (3 × 20 ml), the organic extract washed with water, dried (anhydrous sodium sulfate) and chromatographed over silica gel (100–200 mesh) using light pretroleum containing increasing amount of benzene as eluents; the order of elution being 2,2′-bi[6-substituted-3-methoxycarbonyl-4-oxo-4*H*-1-benzopyran] **5** and a yellow compound 4-hydroxy-6/7-substituted-3-salicyloylxanthone **7**.

6a: (*Meso*) Yield 15%, m.p. 182°C; (Found: C, 64.5; H, 4.5. $C_{22}H_{18}O_8$ requires C, 64.4; H, 4.4%); *m/z* 410(M^+, 5), 205(M^+/2, 11), 204(100), 172(92), 120(40%); υ_{max} / cm^{-1} 3100, 2960, 1660, 1625; δ_H 3.77 (2 × OCH_3,s), 5.46 (2 × H-2,s), 6.41 (2 × H-8, dd, *J* 8.4 and 1.8), 6.93 (2 × H-6, m), 7.27 (2 × H-7, m), 7.52 (2 × H-5, dd, *J* 7.8 and 1.8) and 12.06 (2 × OH, exchangeable, s).

6a: (*dl*) Yield 10%; m.p. 202°C; (Found: C, 64.2; H, 4.5. $C_{22}H_{18}O_8$ requires C, 64.4, H, 4.4%); υ_{max}/cm^{-1} 3100, 2960, 1660, 1640; δ_H 3.82 (2 × OCH_3, s), 5.33 (2 × H-2, s), 6.40 (2 × H-8, dd, *J* 8.1 and 1.2), 6.89 (2 × H-6, m), 7.07 (2 × H-7, m), 7.64 (2 × H-5, dd, *J* 7.8 and 1.8) and 12.32 (2 × OH, exchangeable, s).

6b: Yield 18%; m.p. 198°C (Found: C, 65.5; H, 5.0. $C_{24}H_{22}O_8$ requires C, 65.7; H, 5.1%); *m/z* 406(M^+-MeOH, 10), 374(406-MeOH, 9), 347(3), 219(M^+/2, 95), 187(100), 135(50%); υ_{max}/cm^{-1} 3100, 2960, 1650, 1620; δ_H 2.29 (2 × $ArCH_3$,s), 3.74 (2 × OCH_3, s), 5.40 (2 × H-2, s), 6.32 (2 × H-8, d, *J* 8.1), 7.0.7 (2 × H-7, dd, *J* 8.1 and 1.8), 7.33 (s × H-5, d, *J* 1.8) and 12.07 (2 × OH, exchangeable, s).

6c: Yield 15%; m.p. 220° C; (Found: C, 55.2; H, 3.5. $C_{22}H_{16}Cl_2O_8$ requires C, 55.1; H, 3.4%); ν_{max}/cm^{-1} 3150, 2922, 1650, 1620; δ_H 3.78(2 × OCH_3, s), 5.45(2 × H-2, s), 6.37(2 × H-8, d, *J* 8.7), 7.22 (2 × H-7, dd, *J* 8.7 and 2.6), 7.49(2 × H-5, d, *J*2.6) and 12.00(2 × OH, exchangeable, s).

7a: Yield 25%; m.p. 284°C; (Found: C, 72.5; H, 3.5.$C_{20}H_{12}O_5$ requires C, 72.3; H, 3.6%); ν_{max} / cm^{-1} 3280, 2960, 2860, 1690, 1610; δ_H 7.01(1H, m), 7.16(1H, m), 7.37–7.61 (5H, m), 7.80(H-2, d, *J* 8.1), 8.06 (H-1, d, *J*8.1), 9.17(H-8, dd, *J* 7.8 and 1.8), 10.52(OH, exchangeable, s) and 11.91(OH, exchangeable, s). Its acetate **8a**, white compound, m.p. 186°C; δ_H 2.07(OAc, s), 2.27(OAc, s), 7.22(1H, dd, *J* 8.1 and 1.5), 7.33–7.43(3H, m), 7.51–7.63 (3H, m), 7.67 (H-2, d, *J* 8.1), 8.44 (H-1, d, *J* 8.1), 8.50 (H-8, dd, *J* 8.1 and 1.8).

7b: Yield 30%; m.p. 286°C; (Found: C, 73.1; H, 4.4. $C_{22}H_{16}O_5$ requires C, 73.3; H, 4.5%); *m/z* 360(M^+, 53), 342(M^+ - H_2O, 14), 252(21), 251(100), 225(4), 135(17%); υ_{max} /cm^{-1} 3280, 2922, 2852, 1689, 1608; δ_H (DMSO-d_6) 2.21 (CH_3, s), 2.38(CH_3, s), 6.88(1H, d, *J* 8.3), 7.16–7.34(4H, m), 7.58(H-2, d, *J* 8.3), 7.79 (H-1, d, *J* 8.3), 8.87 (H-8, d, *J* 1.8), 10.24 (OH, exchangeable, s) and 13.15 (OH, exchangeable, s). Its acetate **8b,** white compound, m.p. 194°C; υ_{max} /cm^{-1} 2950, 1790, 1750, 1600, 1510; δ_H 2.05(OAc s), 2.28(OAc, s), 2.36 ($ArCH_3$, s), 2.43 ($ArCH_3$, s), 7.09(1H, d, *J*8.2), 7.28–7.42 (4H, m), 7.64 (H-2, d, *J* 8.1), 8.30 (H-8, d, *J* 1.8), 8.43 (H-1, d, *J* 8.1).

7c: Yield ~ 25% (based on ^{1}H NMR); m.p. is not reportable as was obtained as a mixture of **7a** and **7c.** From ^{1}H NMR of the mixture, signals for **7c** could be separated. δ_H 7.36–7.61 (5H,m), 7.83(H-2, d, *J*8.4), 8.02(H-1, d, *J* 8.4), 9.19(H-8, d, *J* 2.2), 10.48(OH, exchangeable, s) and 11.95 (OH, exchangeable, s).

7d: Yield 35%; m.p. 240°C; (Found: C, 73.2; H, 4.4. $C_{22}H_{16}O_5$ requires C, 73.3; H, 4.5%); *m/z* 360(M^+, 79), 343(M^+-OH, 14), 253(36), 252(100), 224(15), 196(11), 135(19%); υ_{max}/cm^{-1} 3039, 2922, 2852, 1740, 1635, 1583; δ_H 2.42 (CH_3, s), 2.47 (CH_3, s), 6.79 (1H, dd, *J* 8.2 and 1.8), 6.95 (1H, d, *J* 1.8), 7.18–7.20 (2H, m), 7.48 (1H, d, *J* 8.2), 7.72 (H-2, d, *J* 8.3), 8.01 (H-1, d, *J* 8.3), 9.01 (H-8, d, *J* 8.2), 10.77 (OH), exchangeable, s) and 11.75 (OH, exchangeable, s). Its acetate **8d,** a white cotton-like compound, m.p. 212°C υ_{max} / cm^{-1} 2921, 1772, 1735, 1658, 1614; δ_H 2.09 (OAc, s) 2.26(OAc, s), 2.44($ArCH_3$, s), 2.45 ($ArCH_3$, s) 7.01 (1H, d, *J* 1.8), 7.12–7.15(2H, m), 7.22(1H, d, *J* 1.8), 7.49(1H, d, *J* 7.9), 7.59 (H-2, d, *J* 8.1), 8.34(H-8, d, *J*8.4), 8.40(H-1, d, *J*8.1).

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