THE REACTIVITY OF 2-ACETYL (3H)NAPHTHO[2,1-*b*]PYRAN-3-ONE TOWARDS SOME PHOSPHORUS YLIDES: SYNTHESIS OF COUMARINYL[2,1-*b*]-FUSED CYCLIC COMPOUNDS

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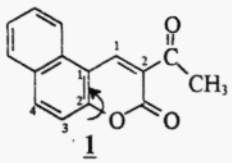
Abstract: Treatment of 2-acetyl (3H)naphtho[2,1-*b*] pyran-3-one **1** with ylides **2a,b** led to the formation of the corresponding [2,1-*b*]-fused substituted benzene **6a,b** and the Wittig products **3a,b**; with ylides **2c,d** afforded, again the corresponding [2,1-*o*]-fused cyclopentadienes **9a,b** and the olefination products **7a,b.** Conversely, compound **1** undergoes conjugated addition reaction with both ylides **10** and **12** to give **11** and **13**, respectively.

Introduction

Polyfunctionally substituted heteroaromatics are of immense importance in biochemistry (1-3). Thus, despite coumarin itself, has very little physiological action upon human being, it has long been recognized the versatile applications of naturally occurring-and synthesized coumaran derivatives (4,5). Previously mentioned fact has encouraged us to synthesize and study the reactions of some novel pyrans by making use of 2-acetyl (3H)naphtho[2,1-*b*]pyran-3-one **1** (also known as 3-acetyl 5,6-benzocoumarin) and some methylenetriphenylphosphoranes (Wittig reagents) **2a-d**, **10** and **12**.



1

$Ph_3P{=}CHCOR$

2a, R= OCH_3
2b, R= OC_2H_5
2c, R= CH_3
2d, R= C_6H_5

$Ph_3P{=}C(Ph)_2$

10

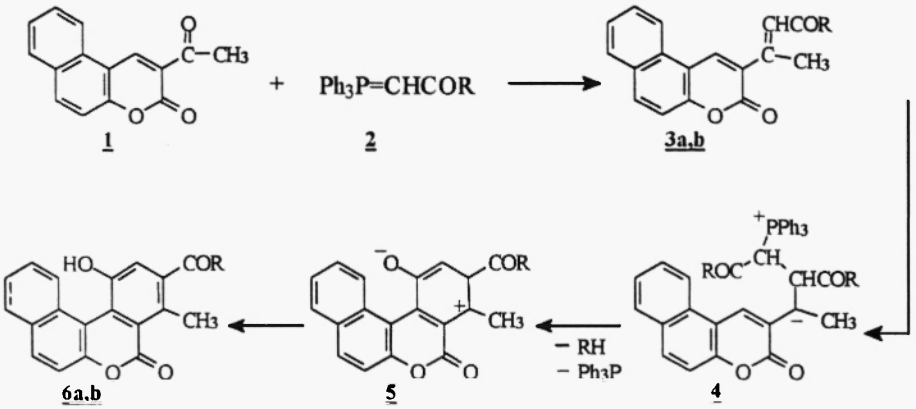
$Ph_3P^+{-}CH_2{-}CH{=}CH_2\ Br^-$

12

Results and Discussion

I. Reaction of **1** *and Alkoxycarbonylmethylenetriphenylphosphorane* **2a,b**. The starting 3-acetyl 5,6-benzocoumarin **1** was synthesized directly from 2- hydroxy-1-naphthaldehyde and ethylacetoacetate in the presence of piperidine as previously reported (6). Treatment of compound **1** with two equivalents of **2a** in boiling toluene containing benzoic acid (as a catalyst) for ~ 36 h afforded the corresponding Wittig product **3a** (*Z*) (48%) together with the substituted dibenzocoumarin **6a** (19%). By a similar treatment of **1** with ylide **2b**, compounds **3b** (38%) and **6b** (14%) were obtained (Scheme 1). Although two isomers (*E* and *Z*), which can differ in the arrangement of the substituents on the carbon-carbon double bond, could be exist for **3**, the *cis* isomer is assigned for the only toutomer obtained in these reactions. The suggested *cis* configuration for compounds **3a** and **3b**, although not established with certainty, are supported by the recorded ^{1}H- and ^{13}C-NMR chemical shifts and

coupling constants of their olefinic- and methyl protons. The determined coupling constants in the recorded ^{1}H-NMR spectrum of **3a** are 2-5 Hz (=CH) and 2-4 Hz ($-CH_3$). The analytical and the spectral data of **3** and **6** agree well with suggested structures. The NMR (7) spectra of compound **6a**



a. R = OCH_3, b. R = OC_2H_5

SCHEME 1

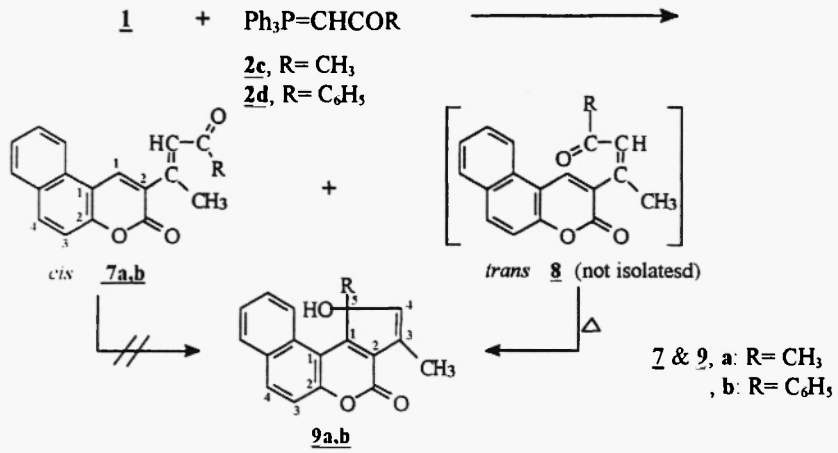
revealed the following assignments: δ_H 2.25 (Ar–CH_3, s), 3.62 (OCH_3, s), 4.75 (OH); δ_C:169.5 (C=O, ester), 162.3 (C=O, coumarin), 151.6 (C–OH), 147.7 (C–CH_3), 61.4 (OCH_3) and at 25.7 ppm (Ar–CH_3).The formation of **6** is assumed to proceed through an initial Wittig olefination of **1** to give the first isolated product **3**. Further Michael addition of a second ylide species **2a,b** to **3** afforded the phosphonium intermediate **4**, which by subsequent elimination of triphenylphosphine and methanol/ethanol moiety yields the cyclointermediate **5**. Rearomatization of the polycyclic system of **5** by the prototropic rearrangement, the substituted pyran **6** was formed (Scheme 1). Besides, it is pointed out that the reaction of **2a,b** with **1** requires a protonating reagent (benzoic acid) (*vide supra*), and the success of this procedure is attributable to the protonation of the carbonyl group making it more electrophilic, and therefore susceptible to nucleophilic attack by the ylide (8).

II. Reaction of 1 with β-Ketoalkylidenephosphoranes 2c,d. Treatment of **1** with acetylmethylenetriphenylphosphorane **2c** (one mol equiv.) in boiling toluene containing benzoic acid for ~ 3 days and separation of the product mixture by column chromatography afforded compounds **7a** and **9a** in 33% and 22%, respectively (Scheme 2). The first product was formulated as 2 [3-acetyl (2H)propylene](3H)naphtho[2,1-*b*] pyran-3-one **7a** and confirmed from its elemental analysis and the spectral data (*cf.* experimental). The second product was found to be a constitution-isomer but not identical with structure **7a** and assigned (3H)naphtho[2,1-*b*]pyran-3-one[2,1-*b*]-3,5-dimethyl-5-hydroxycyclopentadiene **9a** on the basis of its spectral data. Parallel compounds **7b** (28%) and **9b** (18%) (b, R= C_6H_5) were likewise obtained by reacting **1** with benzoylmethylenetriphenylphosphorane (**2d**) under the conditions previously mentioned with **2c**.

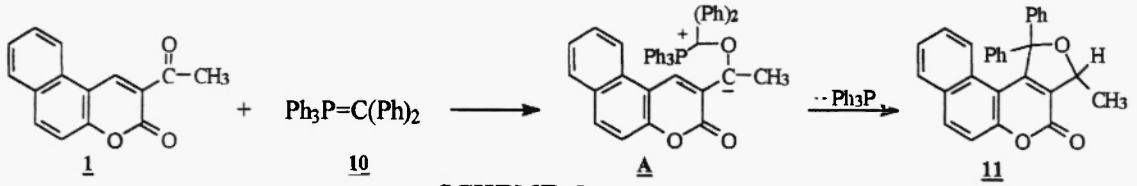
Apparently, formation of compounds **9a,b** involves the intermediate formation of acetyl propylene derivatives of type **8a,b** (essentially in the *trans*- form) which readily cyclises to give **9** upon prototropic rearrangement, meanwhile their *cis* analogues **7** are concurrently produced and do not cyclize to give **9**. Since the formation of **7** and **9** appears to be dependent upon the geometry of the first step, it is safe to state that conversion of **8** to **9** is a stereoselective process (9,10). In favour of

this idea is the finding that **7a** is recovered practically unchanged upon heating alone in boiling toluene even for 20 h.

SCHEME 2



III. Reaction of **1** *and Alkylidenephosphorane* **10**. Furthermore we studied the reaction of **1** with alkylidenephosphorane system. In contrast to the above series **2a-d** of Wittig reagents which undergo mainly the olefination reaction, diphenylmethylenetriphenylphosphorane **3** undergoes a conjugated addition process. Thus, treatment of **1** with the ylide **10**, prepared *in situ* from the corresponding



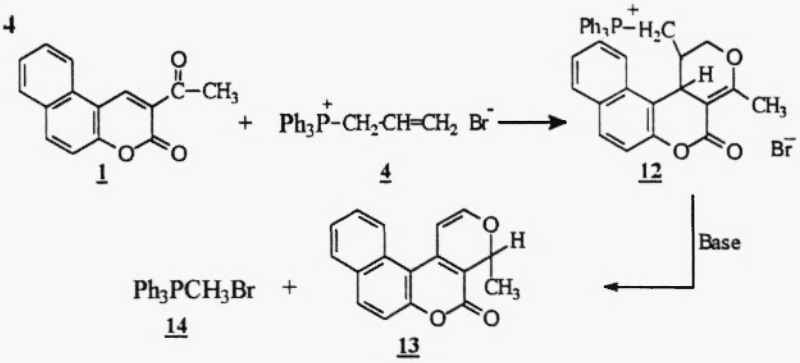
SCHEME 3

bromide salt, afforded the substituted furopyran **11** in 68% yield (Scheme 3). Obviously, formation of the intermediate **A** followed by spontaneous lactonization *via* TTP elimination can account for the formation of **11**. However the latter result is along the line which has been previously explored (11-13) for the tendency of this type of Wittig reagents, alkylidenephosphorane, to undergo addition - elimination process rather than olefination reaction.

IV. Reaction of **1** *with Allyltriphenylphosphonium Bromide* **12**. Treatment **1** with 1 equiv. of NaH in DMF followed by 1 equivalent of **12** yielded the unexpected pyrrole derivative **13** in 22% yield and unidentified products. A mechanism for the formation of the substituted pyrrole **13** can be rationalized as occurring through the attack of oxygen on **12** to generate the salt **A** (Scheme 4), which by extrusion of triphenylmethylphosphonium bromide **14** affords **13**. However, the ready elimination of the salt **14** from **A** occurs through a carbonion mechanism, driven by the resulting gain in aromaticity (14,15).

In conclusion, the reactions between the coumarin derivative **1** and triphenylmethylenephosphoranes are of significant synthetic value, since they can be used for the preparation of several different compounds, depending on the particular reagent present and the reaction conditions.

SCHEME 4



Experimental

Melting points are uncorrected. IR spectra were obtained with a Phillips Infracord Spectrometer Model PU 9712 in KBr. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or [d_6] DMSO as solvent on a Joel-270 MHz Spectrometer. Mass spectra were performed at 70 eV on a Shimadzu GCS-QP 1000 EX Spectrometer provided with a data system.

I. Reaction of 2-Acetyl (3H)naphtho[2,1-b] pyran-3-one 1 and Phosphorus Ylides 2a. A stirred solution of **1** (6) (1 g, 4.2 mmol) and **2a** (2.8 g, 8.4 mmol) in dry toluene (50 ml) containing benzoic acid (0.3 g) was boiled under reflux for 30 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel with hexane-chloroform (9:1→6:4 v/v). The first fraction (up to 9:1) afforded colourless crystals of *(3H)naphtho[2,1-b]pyran-3-one[2,1-b] 1-hydroxy-4-methyl-3-benzoic acid methyl ester* **6a** (266 mg, 19%), mp. 140-142 °C (acetonitrile). Anal. Calcd. for $C_{20}H_{14}O_5$ (334.33): C 71.85, H 4.22. Found: C 71.76, H 4.15. IR (KBr, cm^{-1}): 3408 (OH). 1708, 1647 [2 C(O)]. NMR ($CDCl_3$), δ ppm: δ_H 2.25 (3H, Ar–C**H**$_3$, s), 3.62 (3H, –OC**H**$_3$, s), 4.75 (1H, O**H**, d, exchangeable with D_2O), 7.35-8.22 (7H, Ar–**H**, m); δ_C: 169.5 (**C**=O, ester), 162.3 (**C**=O), 151.6 (**C**–OH), 147.7(**C**–CH_3), 61.4 (OCH_3) and at 25.7 ppm (Ar–**C**H_3). MS: m/z 334 [M^+, 12%].

The second fraction (8:2 v/v), yielded pale yellow crystals of *methyl 2-[(3H)-naphtho[2,1-b]pyran-3-one] but-2-eneoate* **3a** (0.6 g, 48%), mp. 168-170 °C (benzene). Anal. Calcd. for $C_{18}H_{14}O_4$ (294.3): C 73.46, H 4.79. Found: C 73.52, H 4.7. IR (KBr, cm^{-1}): 1709, 1644 [2C(O)], 1569 (C=C, olefin). NMR ($CDCl_3$), δppm: δ_H 2.24 (3H, =C–C**H**$_3$, d, J_{HH}= 2.4 Hz), 3.75 (3H, –OC**H**$_3$, s), 6.15 (1H, =C**H**, d, J_{HH}= 2.5 Hz), 7.42-8.33 (7H, Ar–**H**, m). δ_C: 167.2 (**C**=O, ester), 161.5 (**C**=O, coumarin), 58.7 (OCH_3) and at 25.4 ppm (=C–**C**H_3). MS: m/z 294 [M^+, 100%].

Similarly, the reaction of **1** with ethoxycarbonylmethylenetriphenylphosphorane **2b** afforded colourless crystals of the substituted coumarin **6b** (0.2 g, 14%), mp. 122-124 °C (cyclohexane). Anal. Calcd. for $C_{21}H_{16}O_5$ (348.36): C 72.41, H 4.63. Found: C 72.32, H 4.56. IR (KBr, cm^{-1}): 3397 (OH), 1079, 1644 [2 C(O)]. NMR ($CDCl_3$), δ ppm: δ_H 1.15 (3H, C-C**H**$_3$, t), 2.25 (3H, -C**H**$_3$, s), 4.05 (2H, -OC**H**$_3$, q), 7.43-8.52 (8H, Ar-**H** and O**H**, m); δ_C 166.5 (**C**=O, ester), 161.3 (**C**=O, coumarin), 152.6 (**C**-OH), 147.3 (=**C**-CH_3), 65.7 (OCH_2), 25.7 (Ar-**C**H_3,) and at 14.9 ppm (OC-**C**H_3). MS: m/z 348 [M^+, 45%].

Ethyl 2-[(3H)-naphtho[2,1-b]pyran-3-one] but-2-enoate **3b** (0.3 g. 38%), mp. 147-149 °C (diethyl ether). Anal. Calcd. for $C_{19}H_{16}O_4$ (308.33):C 74.01, H 5.23. Found: C 73.93, H 5.17. IR (KBr, cm^{-1}): 1709, 1645 (2 C=O), 1572 (C=C, exocyclic). ^{1}H NMR ($CDCl_3$), δ_H ppm: 1.23 (3H, C-C**H**$_3$, t), 2.25 (3H, =C-C**H**$_3$, d, J_{HH}= 2.4 Hz), 4.1 (2H, -OC**H**$_2$, q), 6.01 (1H, =C**H**, d, J_{HH}= 2.5 Hz), 7.43-8.32 ppm (7H, Ar-**H**, m). MS: m/z 308 [M^+, 75%].

II. Reaction of 1 and β-Ketoalkylidenephosphoranes 2c,d. To A solution of acetylmethylene-triphenylphosphorane **2c** (1.3 g, 4.2 mmol) in 30 ml toluene was added a solution of compound **1** (1 g, 4.2 mmol) in 30 ml of the same solvent (benzoic acid) and the reaction mixture was refluxed for 3 days. After usual workup, we obtained the products **7a** and **9a**.

(3H)Naphtho[2,1-b]pyran-3-one[2,1-b]-3,5-dimethyl-5-hydroxycyclopentadiene **9a** was eluted first (9.5:0.5 v/v, eluent) as pale yellow crystals (257 mg, 22%), mp. 136-138 °C (diethyl ether). Anal. Calcd. for $C_{18}H_{14}O_3$ (278.3): C 77.68, H 5.07. Found: C 77.76, H 5.01. IR (KBr, cm^{-1}): 3335 (OH), 1710 (C=O, coumarin). NMR ($CDCl_3$), ppm: δ_H 0.67, 2.51 (6H, 2-C**H**$_3$, 2s), 7.37-8.36 (7H, rings-**H**, m), 9.12 (1H, -O**H**, changeable with D_2O); δ_C: 160.1 (**C**(O), coumarin), 74.7 (**C**(OH)CH_3), 25.4 (-**C**H_3) and at 18.6 ppm (HOC-**C**H_3). MS: m/z 278 [M^+, 100%].

2[3-Acetyl (2H)propylene](3H)naphtho[2,1-b] pyran-3-one **7a** was eluted next (9:1 v/v, eluent) as pale yellow crystals (550 mg, 33%), mp. 148-150 °C (cyclohexane). Anal. Clacd. for $C_{18}H_{14}O_3$ (278.3): C 77.68, H 5.07. Found: C 77.6, H 4.99. IR (KBr, cm^{-1}): 1709 (C=O, coumarin), 1672 (C=O, acetyl), 1616 (C=C, exocyclic). ^1H NMR ($CDCl_3$), δ_H ppm, 2.15,2.25 (6H, 2-C**H**$_3$, 2s), 6.83 (1H, =C**H**, exocyclic, s), 7.4-8.26 (7H, Ar-**H**, m), δ_C: 197.9 (**C**(O)CH_3), 159.5 (**C**(O), coumarin), 31.3 (C(O)**C**H_3). MS: m/z 278 [M^+, 100%].

Compounds **7b** and **9b** were likewise obtained and characterized upon reacting **1** with **2d** under above same conditions and workup.

(3H)Naphtho[2,1b]pyran-3-one[2,1-b]-3-methyl-5-hydroxy-5-phenylcyclopentadiene **9b** was obtained (1:1, v/v, eluent) as yellow crystals (257 mg, 18%), mp. 178-180 °C ($CHCl_3$/diethyl ether, 1:1). Anal. Cacld. for $C_{23}H_{16}O_3$ (340.38): C 81.16, H 4.74. Found: C 81.27, H 7.65. IR (KBr, cm^{-1}): 3331 (OH), 1712 (C=O, coumarin). NMR ($CDCl_3$), δ_H ppm: 2.62 (3H, -C**H**$_3$, s), 7.36-8.54 (11H, Ar-**H**, m), 9.35 ppm (1H, O**H**). MS: m/z 340 [M^+, 100%].

2[3-Benzoyl(2H)propylene](3H)naphtho[2,1b]pyran-3-one **7b** was eluted next (8:2, v/v, eluent) as yellow crystals (0.4 g, 28%), mp. 150-152 °C (benzene). Anal. Calcd. for $C_{23}H_{16}O_3$ (340.38): C 81.16, H 4.74. Found: C 81.05, H 4.68. IR (KBr cm^{-1}): 1707, 1657 (2 C=O), 1593 (C=C, exocyclic). NMR ($CDCl_3$), δ_H ppm: 2.4 (3H, C**H**$_3$, s), and at 7.32-8.51 ppm (12H, Ar-**H** & exocyclic =C**H**, m). MS: m/z 340 [M^+, 100%].

Action of heat on compounds 7a,b. Compound **7a**, taken as a representative example, (250 mg) was refluxed in dry toluene (30 ml) for 20 h. After evaporation of the solvent to dryness *in a vacue*, the residual substance was recrystallized from cyclohexane to give pale yellow crystals (215 mg, > 85%) and proved to be unchanged **7a** (mp., mixed mps. and comparative IR spectra).

III. Reaction of 1 and Diphenylmethylenetriphenylphosphorane 10. Into a well dried three necked flask containing 0.5 g sodium metal dissolved in 50 ml absolute alcohol, diphenylmethyltriphenylphosphonium bromide (2.3 g, 4.5 mmol) was added portionwise. The reaction mixture was stirred at r. t. for 1 h followed by addition of **1** (1 g, 4.2 mmol) and then heated under reflux for 35 h. The product mixture was concentrated to 20 ml, diluted with 20 ml distl. H_2O, acidified with conc. HCl and then extracted with two-100 portions of $CHCl_3$. The $CHCl_3$ extracts were combined, backwashed with 100 ml of H_2O, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* under reduced pressure. The residue was chromatographed on silica gel with hexane-$CHCl_3$. Elution with pure hexane afforded TPP. Fraction up to (4:6 v/v) eluted pale yellow crystals of (3H)naphtho[2,1-*b*]pyran-3-

one[2,1-*b*]-2-hydro-2-methyl-5,5-diphenylfuran **11** (0.7 g, 40%), mp. 125-127 °C (benzene). Anal. Calcd. for $C_{28}H_{20}O_3$ (404.47): C 83.15, H 4.98. Found: C 83.23, H 4.92. ^{1}HNMR ($CDCl_3$), δ ppm: 0.95 (3H, $-CH_3$, d, J_{HH}= 6.5 Hz), 4.15 (1H, C**H**, q), 7.17-7.82 ppm (16H, Ar-**H**, m). MS: m/z 404 [M^+, 33%].

***IV. Reaction of* 1 *and Allyltriphenylphosphonium Bromide* 12.** To a slurry of 240 mg of NaH dispersion (57% in mineral oil) in 10 ml of dry DMF was added dropwise 1.2 g (5 mmol) of **1** in 20 ml of DMF. The deeply coloured reaction mixture was stirred at r. t. untill all hydrogen evolution had ceased, and the salt **12** (1.9 gm, 5.2 mmol) was added at once. After stirring for 12 h the reaction mixture was poured into 300 ml of H_2O and extracted with 2-100 ml portion of $CHCl_3$. The $CHCl_3$ extracts were combined, backwashed with 100 ml of H_2O, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel with hexane-$CHCl_3$. Fraction up to (9:1 v/v) eluted pale yellow crystals of (3H)naphtho[2,1-*b*] pyran-3-one[2,1-*c*] 2,2-methylhydropyrrole **13** (240 mg, 22%), mp. 110-112 °C (pentane). Anal. Calcd. for $C_{17}H_{12}O_3$ (264.28): C 77.26, H 4.57. Found: C 77.33, H 4.46. IR (KBr, cm^{-1}): 1707 (C=O, coumarin). ^{1}H NMR, δ ppm: 0.93 (3H, $-CH_3$, d, J_{HH}= 6.5 Hz), 4.08 (1H, C**H**, q), 7.16-7.88 (8H, Ar–**H**, m). MS: m/z 264 [M^+, 65%].

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