Monatshefte für Chemie 135, 817–821 (2004)
DOI 10.1007/s00706-003-0138-6

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

A Route to the Synthesis of Novel Coumarins

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Received September 5, 2003; accepted September 29, 2003
Published online February 5, 2004

Summary. The 1:1:1 adduct which originates from the reaction of triphenylphosphine, dialkyl acetylenedicarboxylate, and 3-formyl-4-hydroxycoumarin undergoes an intramolecular *Wittig* reaction to provide a series of unique 2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-ones (pyranocoumarins).

Keywords. Coumarin; Pyran; Intramolecular *Wittig* reaction; Acetylenic esters; 2*H*,5*H*-pyrano [3,2-*c*][1]benzopyran-5-one.

Introduction

Coumarin is the structural motif of many natural and synthetic compounds which endows them with a wide range of biological activities. Given the development of coumarins as photosensititers [1], anti-*HIV* agents [2], antibiotics [3], rodenticides, or oral anticoagulants [4], there has been continuous interest in the synthesis of these materials. Though many efforts have been paid to the synthesis of 3-substituted-4-hydroxycoumarin derivatives, there is a shortage of studies on the synthesis of angularly or linearly pyran-annulated tricyclic analogues [5]. Several derivatives of pyran or fused pyran ring systems have shown relevant pharmaceutical properties [6].

In the present paper we describe an efficient and simple synthesis of the novel angular pyranocoumarins **4** functionalized at the addended pyran ring.

Results and Discussions

As outlined in Scheme 1, we approached the synthesis through a simple preparation of 3-formyl-4-hydroxycoumarin (**2**) under microwave irradiation. Thus, in the presence of a catalytic amount of *p*-toluenesulfonic acid, a mixture of 4-hydroxycoumarin and triethyl orthoformate quickly reacted under microwave and solvent-

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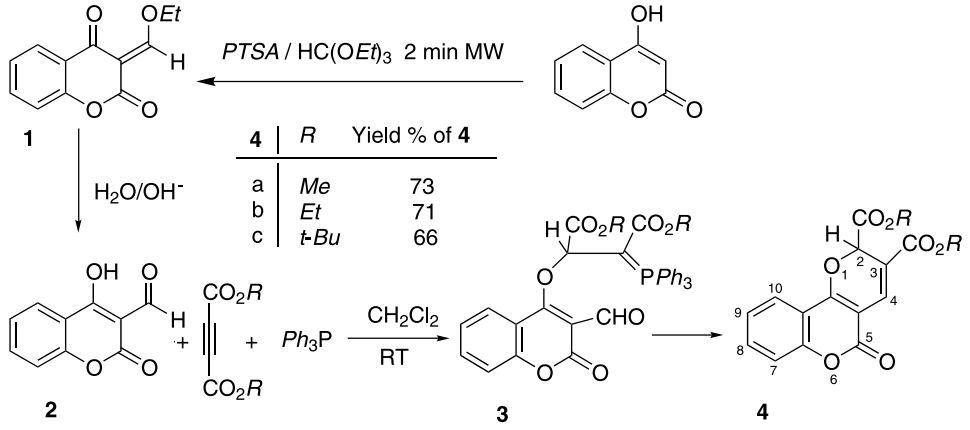
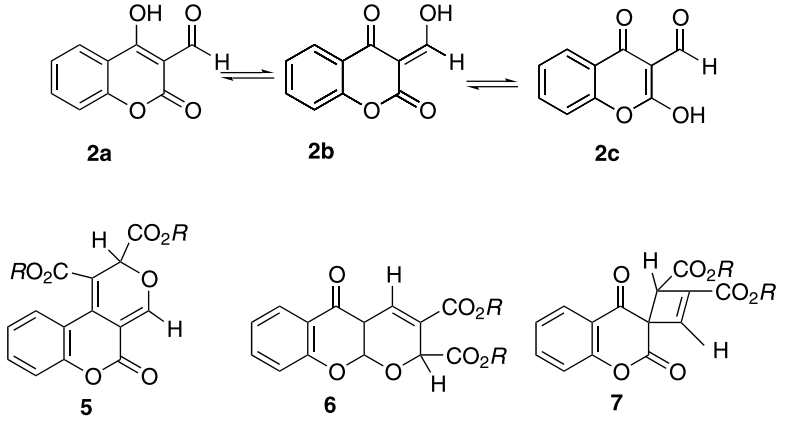


Scheme 1

free condition to provide **1**. The crude reaction product on mild hydrolysis gave the desired 3-formyl-4-hydroxycoumarin (**2**) in 68% yield. However, this method works with much lower amounts of orthoester and takes shorter reaction time than the conventional heating method [7] providing practically the same yield (ca. 67%).

The formyl derivative **2** was reacted with an *in situ* generated 1:1 adduct of triphenylphosphine and dialkyl acetylenedicarboxylate. Thereby good yields of the dialkyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one-2,3-dicarboxylates (pyranocoumarins) **4a**–**4c** were obtained. The reaction can be rationalized on the basis of the well-known chemistry of trivalent phosphorus nucleophiles [8]. Addition of triphenylphosphine to acetylenic ester results in a zwitterionic 1:1 adduct which upon attraction of a proton from **2** and concomitant addition of the thus formed 3-formylcoumarin-4-hydroxylate anion produces the key intermediate phosphorane **3**. The reaction ultimately entails with an intramolecular *Wittig* reaction of the postulated phosphorane **3** [9].

Only triphenylphosphine oxide and **4** were obtained from the tarry residue by column chromatography. It is conceivable to consider **2** as three existing tautomers,



Scheme 2

namely **2a**, **2b**, and **2c** (Scheme 2), therefore, its nucleophilic attack potentially can occur at either of each carbonyl O-atoms or even at C-3 resulting in compounds **4**, **5**, **6**, or **7**. However, the structures of separated products were identified as **4a**–**4c** according to their IR, ^{1}H, and ^{13}C NMR, as well as mass spectral data. The regioselectivity of this reaction may be partially ascribed to the predominant existence of **2a** in aprotic solvents [10].

The IR spectra of **4a**–**4c** contain bands at $\bar{\nu} = 1712$–$1735\,\mathrm{cm}^{-1}$, which are characteristic of the stretching vibrations of the coumarinic and ester C=O bonds. Thus the formation of **7** could be excluded. The ^{1}H NMR spectrum of **4a**, *e.g.*, displayed the characteristic downfield shift of C_{10}–H proton at $\delta = 7.84$ ppm as a *dd* with ^{3}J and ^{4}J values of 7.9 and 1.3 Hz. The multiplet at $\delta = 7.6$ ppm is readily distinguished as the C_8–H resonance, because it has a ^{4}J value of 1.3 Hz corresponding to a meta coupling with C_{10}–H. In the aromatic region C_7–H and C_9–H revealed at $\delta = 7.36$–7.40 ppm an overlapping doublet and triplet. There were also four singlets in the spectrum that were readily recognized as arising from two CH_3–O ($\delta = 3.80$ and 3.86 ppm), O–CH–CO_2Me ($\delta = 4.7$ ppm), and olefinic C_4–H ($\delta = 7.85$ ppm) protons. The ^{13}C NMR spectrum of **4a** showed sixteen distinct resonances in agreement with the structure of **4**. Partial assignments of these signals are given in Experimental. Since a signal referring to a quaternary aliphatic carbon is expected for **6** and, expectedly, one member of the five down-field resonances should appear as an N*O*E enhanced signal arising from the =CH–O moiety for **5**, the absence of such peaks in the spectrum leads to exclusion of the corresponding structures. The ^{1}H and ^{13}C NMR spectra of **4b** and **4c** are similar to those of **4a** except for the ester groups, which exhibit characteristic signals with appropriate chemical shifts. In the ^{1}H NMR spectrum of **4b** the methyl protons experience similar couplings with the diastereotopic protons of methylene moieties, so they appear as triplets, but the methylenic protons because of embedding the geminal coupling appear as multiplets (two ABX_3 systems). The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values. Any initial fragmentations involved the loss of the ester moieties.

In conclusion we have found a simple and efficient route to the synthesis of pyrano[3,2-*c*][1]benzopyrans **4a**–**4c**, which are not obtained easily or as the sole products by other methods [11]. These functionalized products are amenable to further transformations and we anticipate that they may have important applications in medicinal and synthetic organic chemistry.

Experimental

Melting points were measured on a Mettler FP5. Elemental analyses (C, H) were conducted using a Heraeus CHN–O-Rapid analyzer. The results were found to be in good agreement (±0.2%) with the calculated values. IR Spectra were obtained with KBr wafers on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$-*TMS*, with a Brucker DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Microwave irradiations were carried out in a 1000 W domestic oven at 2450 MHz. Chemicals were obtained from Merck & Fluka companies and were used without further purification. Chromatography columns were prepared from Merck silica gel 70–230 mesh.

3-Formyl-4-hydroxycoumarin (**2**)

A mixture of 6.2 mmol of 4-hydroxycoumarin, 7 cm^3 of triethyl orthoformate, and 0.02 g of *p*-toluenesulfonic acid monohydrate was placed in a 50 cm^3 beaker. The beaker was covered with a stemless funnel and irradiated in the microwave oven for 1 min at 240 W and then 1 min at 180 W. The resultant residue was cooled to room temperature, the solvent was decanted, and the residue was dissolved in 15 cm^3 of 0.15 *N* Na_2CO_3 solution. It was poured into a separatory funnel, acidified to $pH = 4$, and extracted with 2×20 cm^3 of Et_2O. The crystals separated from evaporation of ethereal solution were recrystalized from *n*-hexane to obtain 68% of **2** as yellow needles, mp 138–139°C (Ref. [7] 136–137°C).

General Procedure for the Preparation of Dialkyl 2H,5H-pyrano[3,2-c][1]benzopyran-5-one-2,3-dicarboxylates ***4a–4c***

To a magnetically stirred solution of 0.38 g of **2** (2 mmol) and 0.52 g of triphenylphosphine (2 mmol) in 6 cm^3 of CH_2Cl_2 a solution of 2 mmol of dialkyl acetylenedicarboxylate in 4 cm^3 of CH_2Cl_2 was added dropwise over 10 min at −10°C. The reaction mixture was then allowed to warm up to room temperature and stirred for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using *n*-hexane:ethyl acetate (3:1) as eluent. The products were crystallised from the effluent solution and were recrystallised in *n*-hexane:ethyl acetate = 4:1.

Dimethyl 2H,5H-pyrano[3,2-c][1]benzopyran-5-one-2,3-dicarboxylate (**4a**, $C_{16}H_{12}O_7$)

Yield 73%, colorless crystals, mp 196–197°C (*n*-hexane:ethyl acetate); IR (KBr): $\bar{\nu} = 3086$, 2930 (C–H), 1733 and 1718 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.85$ (s, 4-H), 7.84 (dd, $J = 7.9$ and 1.3 Hz, 10-H), 7.63 (dt, $J = 1.3$ and 7.9 Hz, 8-H), 7.39 (d, $J = 7.9$ Hz, 7-H), 7.38 (t, $J = 7.9$ Hz, 9-H), 4.71 (s, 2-H), 3.86 and 3.80 (2s, $2CH_3$–O) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.8$, 165.4, 161.2 (3C=O), 156.1, 153.0, 113.7, 109.8, 101.0 (5C), 149.5, 133.4, 125.0, 123.2, 117.3 (5CH), 53.5 and 36.5 ($2CH_3$), 52.7 (C-2) ppm; MS: m/z (%) = 316 (M^+, 11), 257 ($M^+ - CO_2CH_3$, 100), 227 (4), 214 (5).

Diethyl 2H,5H-pyrano[3,2-c][1]benzopyran-5-one-2,3-dicarboxylate (**4b**, $C_{18}H_{16}O_7$)

Yield 71%, colorless crystals, mp 177–178°C (*n*-hexane:ethyl acetate); IR (KBr): $\bar{\nu} = 3100$, 2992 (C–H), 1720 (br, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.83$ (s, 4-H), 7.82 (dd, $J = 7.8$ and 1.3 Hz, 10-H), 7.62 (dt, $J = 1.3$ and 7.8 Hz, 8-H), 7.37 (d, $J = 7.8$ Hz, 7-H), 7.36 (t, $J = 7.8$ Hz, 9-H), 4.68 (s, 2-H), 4.35–4.20 (m, $2CH_2$–O), 1.35 (t, $J = 7.2$ Hz, CH_3), 1.31 (t, $J = 7.1$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 171.3$, 165.0, 161.2 (3C=O), 156.0, 153.0, 113.7, 110.1, 101.0 (5C), 149.2, 133.3, 124.9, 123.1, 117.2 (5CH), 62.4 (C-2), 61.7 and 36.7 ($2CH_2$–O), 14.6 and 14.4 ($2CH_3$) ppm; MS: m/z (%) = 345 (M^+, 11), 271 ($M^+ - CO_2Et$, 100), 243 (271 − CH_2=CH_2, 50), 227 (5).

Di-tert-butyl 2H,5H-pyrano[3,2-c][1]benzopyran-5-one-2,3-dicarboxylate (**4c**, $C_{22}H_{24}O_7$)

Yield 66%, colorless crystals, mp 129–130°C (*n*-hexane:ethyl acetate); IR (KBr): $\bar{\nu} = 3097$, 2994 (C–H), 1720 (br, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.78$ (d, $J = 7.9$ Hz, 10-H), 7.71 (s, 4-H), 7.57 (t, $J = 7.9$ Hz, 8-H), 7.32 (d, $J = 7.9$ Hz, 7-H), 7.31 (t, $J = 7.9$ Hz, 9-H), 4.53 (s, 2-H), 1.54 (s, CMe_3), 1.46 (s, CMe_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 170.4$, 164.1, 161.3 (3C=O), 156.0, 153.0, 113.9, 111.6, 101.5, 82.7, 82.4 (7C), 148.5, 133.1, 124.8, 123.1, 117.2 (5CH), 37.8 (C-2), 28.5 ($3CH_3$), 28.2 ($3CH_3$) ppm; MS: m/z (%) = 401 (M^+, 2), 345 ($M^+ - C_4H_8$, 10), 299 ($M^+ - CO_2CMe_3$, 26), 289 (20), 243 (299 − CH_2=CMe_2, 100), 149 (14).

Acknowledgments

We would like to thank the research council of Guilan University for financial support of this work.

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