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ScienceDirect
Tetrahedron 63 (2007) 8298–8304
Tetrahedron

Synthesis of novel pyridocoumarins and benzo-fused 6-azacoumarins

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Received 5 April 2007; revised 9 May 2007; accepted 24 May 2007
Available online 2 June 2007

Abstract—Benzo[7,8]-fused 6-azacoumarins are prepared from 4-quinolinol by treatment with PPh_3 and DMAD, or from 3-formyl-4-quinolinol by Wittig reaction with carbalkoxyalkylidene(triphenyl)phosphoranes. Angular pyridocoumarins are prepared from 8- or 6-quinolinols with PPh_3 and DMAD, or from the reactions of 5,6- or 7,8-quinolinediones with carbalkoxymethylene(triphenyl)phosphoranes.

1. Introduction

Coumarins fused with heterocycles and aza-analogues of coumarins have received increasing attention due to their potential biological activities.[1] In particular, those coumarins fused to pyridines have been reported to possess antiallergic,[2] antidiabetic,[3] and analgesic[4] properties. Sliwa et al.[5] reported the synthesis of some 5-azacoumarins by the treatment of 2-formyl-3-hydroxypyridines with phosphorus ylides $Ph_3P{=}C(R)COOR'$, and further thermal isomerization in the presence of pyridinium chloride of the initially obtained (*E*)-3-(3-hydroxypyridin-2-yl)propenoates. Queguiner et al.[6] synthesized 6-azacoumarin in 45% overall yield by a Knoevenagel reaction from a mixture of 2-formyl-3-hydroxypyridine, malonic acid, aniline and treatment of the (*E*)-3-(4-hydroxypyridin-3-yl)propenoic acid obtained with pyridinium chloride at 220 °C. Yavari et al.[7] prepared 8-amino-4-methoxycarbonyl-7-azacoumarins from the reaction of 2-amino-3-hydroxypyridine with dimethylacetylenedicarboxylate (DMAD) and triphenylphosphine (PPh_3) via the aromatic electrophilic substitution reaction between the conjugate base of phenol and the vinyltriphenylphosphonium salt formed. 3*H*-Pyrano[3,2-*f*]quinoline-3-one is a known pyridocoumarin and was synthesized in 14% yield by means of a Skraup reaction, carried out on 6-nitrocoumarin.[8]

In the interest of synthesizing new coumarin ring systems for possible evaluation as biologically active compounds, we have prepared a variety of coumarins 7,8-fused onto furan,[9] pyran,[9–12] dioxole,[9,13] [1,4]oxazine,[14,15] and oxazole[16,17] rings. In continuation of this work, we wish to report here the synthesis of some benzo-fused 6-azacoumarins, as well as the synthesis of some angular coumarins 5,6- or 7,8-fused onto a pyridine ring. The preparations of azacoumarins are depicted in Schemes 1 and 2, while the preparations of pyridocoumarins are depicted in Schemes 3 and 4.

2. Results and discussion

Treatment of 2-methyl-4-hydroxyquinoline (**1**)[18] with DMAD (**2**) and PPh_3 (**3**) in toluene under reflux, and separation of the reaction mixture by column chromatography afforded dimethyl 2-(4-hydroxy-2-methyl-3-quinolinyl)-2-butenedioate (**7**) in 65% yield, as well as trace amounts of methyl 5-methyl-2-oxo-2*H*-pyrano[3,2-*c*]quinoline-4-carboxylate (**8**).

The pathway depicted in Scheme 1 was suggested in the literature for the direct formation of coumarins from other phenols[7,19,20] in a similar treatment with **2** and **3**. The isolation of an *o*-hydroxyarylbutenedioate, similar to **7**, has not yet been reported in the published reactions of other phenols. The ^1H NMR spectrum of **7** exhibited two 3H singlets at δ 3.62 and 3.72 for the methoxy protons, a singlet at δ 7.14 (1H) for the olefinic proton and a broad 1H singlet at δ 10.06 for the HO-proton (removed by addition of D_2O) in agreement with the proposed structure **7**. The ^{13}C NMR spectrum showed two ester carbonyl carbons at δ 165.1 and 165.3 ppm.

When compound **7** was heated at 150–160 °C for 26 h, it remained unchanged. By further heating at 200–205 °C for an additional 4 days, it transformed to methyl 5-methyl-2-oxo-

Keywords: Pyridocoumarins; Benzo[7,8]6-azacoumarins; Wittig reaction; PPh_3; DMAD.
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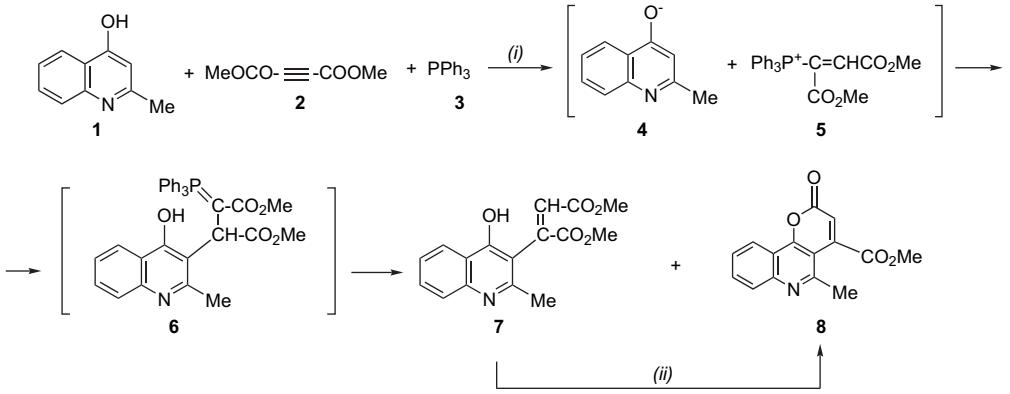
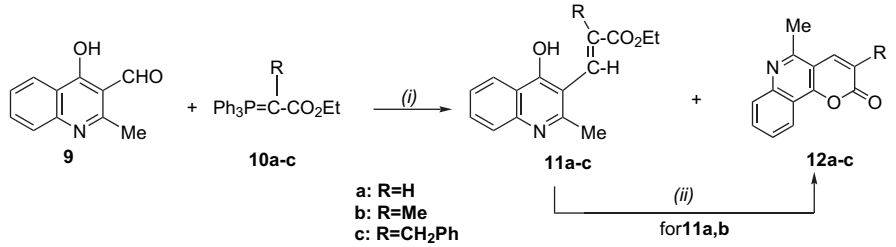
doi:10.1016/j.tet.2007.05.102



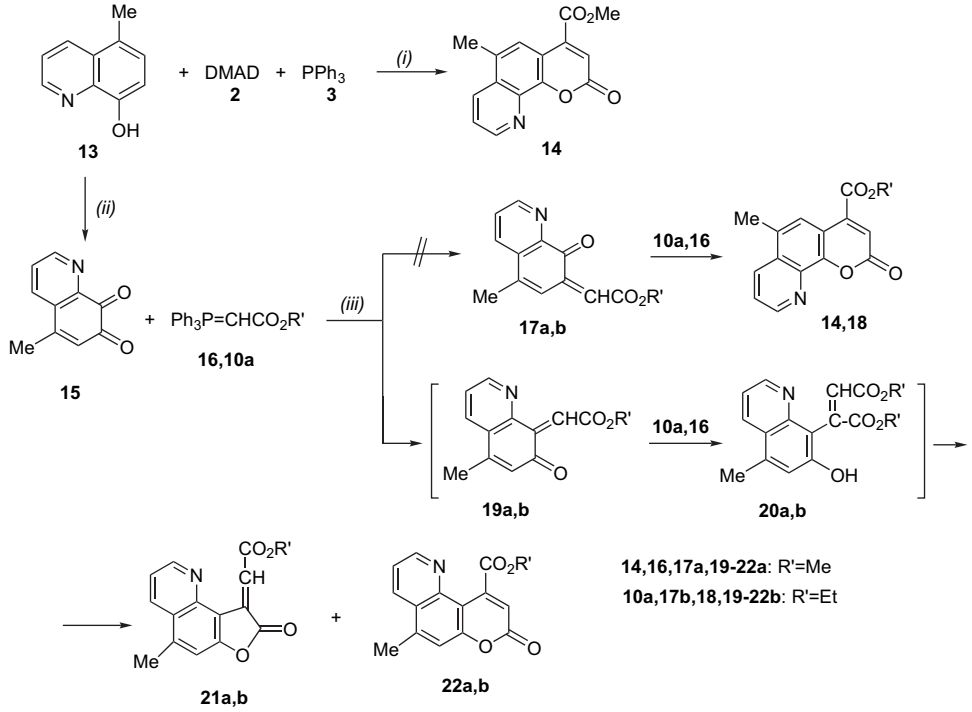
Scheme 1. Reagents and conditions: (i) toluene, reflux; (ii) 200–205 °C.



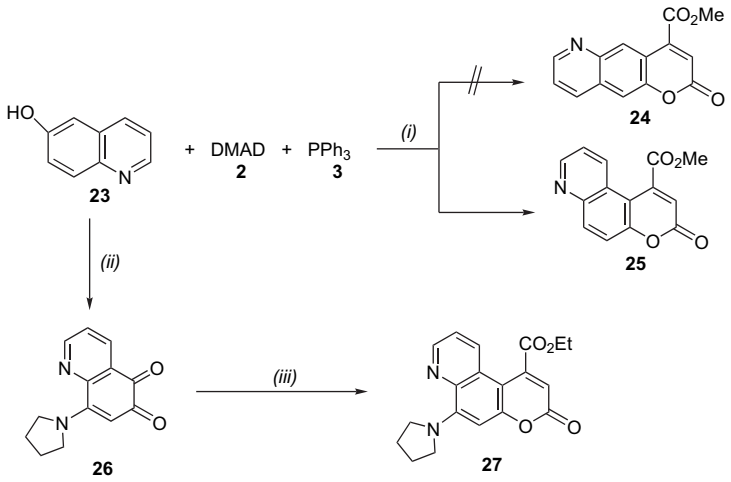
Scheme 2. Reagents and conditions: (i) dry toluene, 60 °C (48 h) or reflux (11 days or 6 days); (ii) 210–230 °C (66 h) or 180–185 °C (4 days).

2*H*-pyrano[3,2-*c*]quinoline-4-carboxylate **8** in 10% yield, which sublimed in pure form in the upper part of the apparatus. The analytical and spectral data of the product agree with the structure **8** suggested. Its ^{1}H NMR spectrum showed one 3H singlet at δ 4.06 for only one methoxy group, and a singlet (1H) at δ 6.56 for 3-H. The IR spectrum exhibited carbonyl absorptions at 1725 and 1706 cm^{-1}. In the ^{13}C NMR spectrum one carbon appeared for the coumarin carbonyl (δ 160.9 ppm) and one carbon for the carbonyl ester moiety (δ 167.7 ppm).

Next, we transformed compound **1** to 3-formyl-4-hydroxyquinaldine (**9**)[21] and studied its reactions with phosphorus ylides **10a**–**c**, as depicted in Scheme 2.



Scheme 3. Reagents and conditions: (i) toluene, reflux; (ii) Fremy's salt; (iii) DCM, reflux.



Scheme 4. Reagents and conditions: (i) toluene reflux; (ii) pyrrolidine, $Cu(OCOMe)_2$, O_2; (iii) DCM, reflux.

Treatment of hydroxyaldehyde **9** with equimolar amount of ylide **10a** in dry toluene at 60 °C for 48 h afforded ethyl 3-(4-hydroxy-2-methylquinolinyl)-2-propenoate (**11a**) as yellow crystals, in 72% yield. Separation of the filtrate by column chromatography gave 5-methyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (**12a**) in 7% yield. Efforts for further lactonization of the isolated hydroxyester **11a** to **12a**, by refluxing a solution of it in xylene or by irradiation of a benzene solution under sunlight, failed. The desired lactonization was achieved by heating the solid **11a** without solvent at 210–230 °C for 66 h. The produced azacoumarin **12a** was sublimed and collected in pure form, from the upper parts of the apparatus, in 37% yield. The ^{1}H NMR spectrum of compound **11a** showed one doublet at δ 7.74 (J=14.8 Hz, 1H) for the β-olefinic proton, characteristic for their (*E*)-configuration, in good agreement with the resistance of the product to lactonization in lower temperature.

The isolation of compound **12a** as byproduct of the reaction between **9** and **10a** performed at 60 °C, can be explained if we consider that the (*Z*)-isomer of **11a** was also formed, as byproduct, from the Wittig reaction and was easily cyclized to lactone **12a**. When the same reaction was carried out by heating the mixture of **9** and **10a** in toluene in a commercial microwave oven (800 W) for 3 min, compounds **11a** and **12a** were again obtained in lower yields, 16 and 2%, respectively.

The reaction between equimolar amounts of **9** and the ylide **10b** was carried out in dry toluene. After an unsuccessful attempt at 60 °C for 24 h, the mixture was then refluxed for 11 days to give a precipitate of ethyl 3-(4-hydroxy-2-methyl-3-quinolinyl)-2-methyl-2-propenoate (**11b**) in 76% yield. Separation of the filtrate by column chromatography gave 3,5-dimethyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (**12b**) in 8% yield. The same product was also obtained in 66% yield after prolonged heating for 4 days of **11b** at 180–185 °C. The product was sublimed and collected like **12a**.

Similarly, the reaction of **9** with ylide **10c** was performed in dry toluene under reflux for 6 days, since a previous effort at 60 °C, for 24 h, was unsuccessful. The reaction mixture was then subjected to column chromatography to give first 3-benzyl-5-methyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (**12c**) (7%), followed by the elution of ethyl 2-benzyl-3-(4-hydroxy-2-methyl-3-quinolinyl)-2-propenoate (**11c**) (17%).

NOE experiments revealed the *E*-configuration for the isolated compound **11b** (3.6% interaction between two methyl protons) in agreement with its resistance to lactonization. It is not clear in these cases if the direct isolation of coumarins **12b**,**c** is an evidence for the formation of the (*Z*)-hydroxyesters **11b**,**c** also as byproducts from the Wittig olefination of **9** with **10b**,**c**, or whether the higher temperature applied in these reactions leads to the further partial lactonization of their (*E*)-isomers. The analytical and spectral data of compounds **11b**,**c** and **12b**,**c** are in good agreement with the structures suggested for them. Furthermore, compounds **11b**,**c** showed absorptions for –OH (3434, 3467 cm^{-1} in the IR, and δ 11.34, 9.24 ppm in the ^{1}H NMR spectra, respectively) and –OEt groups [δ 4.23 (q), 1.33 (t) and 4.11 (q), 1.16 (t) in the ^{1}H NMR and 13.8, 59.9 and 14.1, 60.7 in the ^{13}C NMR spectra, respectively].

Treatment of 5-methyl-8-quinolinol (**13**) with DMAD (**2**) and PPh_3 (**3**) in refluxing toluene for 5 h, and separation of the reaction mixture by column chromatography gave methyl 6-methyl-2-oxo-2*H*-pyrano[3,2-*h*]quinolin-4-carboxylate (**14**) in 76% yield (Scheme 3), obviously via a reaction sequence similar to that depicted in Scheme 1.

Next, we oxidized the quinolinol **13** to the known 5-methyl-7,8-quinolinedione (**15**).[22] It is known that *o*-quinones react with carbalkoxymethylene(triphenyl)phosphoranes to give 4-carbalkoxy-substituted coumarins,[10,12,13,23,24] along with alkyl(2,3-dihydro-2-oxobenzo[*b*]furan-3-ylidene)acetates, in some cases. An intermediate, the very reactive *o*-quinone methanide **19a**,**b**, is initially formed by Wittig olefination of the carbonyl with the more electrophilic carbon atom, followed by Michael addition of a second ylide species and PPh_3 elimination to give an *o*-hydroxybutenedioate. A similar intermediate is also obtained from the reaction of phenols with DMAD and PPh_3, but in the second case the butenedioate substituent is introduced as a vinyltriphenylphosphonium electrophile, via an aromatic electrophilic substitution reaction, in the most nucleophilic *o*-position of the conjugate base of the phenol, if both the *o*-positions

are free. δ-Lactonization of these intermediates affords the coumarin derivatives, as it is depicted in Schemes 1 and 2.

First we studied the reaction of quinone **15** with methoxycarbonylmethylene(triphenyl)phosphorane **16** in order to investigate if the reaction again affords the pyridocoumarin **14**, via an initial olefination of 7-CO, or if it leads to the formation of the desired isomer methyl 5-methyl-8-oxo-8*H*-pyrano[2,3-*h*]quinoline-10-carboxylate (**22a**), via the initial olefination of the 8-CO, since the latter is considered to be more reactive, due to the −I effect of the nitrogen atom.

Treatment of **15** with **16** in methylenechloride under reflux for 2 h, and separation of the reaction mixture by column chromatography afforded first methyl 2-[5-methyl-8-oxo-furo[2,3-*h*]quinolin-9(8*H*)-ylidene]acetate (**21a**) (14%) and then compound **22a** (20%). Compound **14** was not isolated or detected in the reaction mixture. Similarly, the reaction of **15** with ylide **10a** gave ethyl 2-[5-methyl-8-oxo-furo[2,3-*h*]quinolin-9(8*H*)-ylidene]acetate (**21b**) and ethyl 5-methyl-8-oxo-8*H*-pyrano[2,3-*h*]quinoline-10-carboxylate (**22b**) in 22 and 39% yield, respectively, while compound **18** was not detected or isolated from the reaction mixture.

The distinction between the γ- and δ-lactonization products **21** and **22** was initially based on their IR spectra, since the carbonyl absorption of the five-membered lactones appears at a higher cm^{-1} value than those of the six-membered. On the other hand, in all the similar previous reactions studied by us,[10,13,14] the γ-lactonization products were eluted before the coumarins, and obtained in lower yields and had higher mp's. In relation to these previous observations, compounds **21a**,**b** absorb at 1740 cm^{-1} were eluted first, and were formed in lower yield and have higher mp's, while compounds **22a**,**b** show in their IR spectra absorption at 1725 and 1715 cm^{-1}, respectively, and have lower mp's.

The ^1H NMR spectra of **22a**,**b** are almost identical to each other with exceptions of the absorptions of their –OMe and –OEt protons, while the ^1H NMR spectrum of compound **14** differs substantially from the ^1H NMR spectra of both isomeric products **21a** and **22a**.

Next, we studied the reaction of 6-quinolinol (**23**) with DMAD and PPh_3 in refluxing toluene, which resulted in the formation of the angular methyl 3-oxo-3*H*-pyrano[3,2-*f*]quinoline-1-carboxylate (**25**) in 93% yield (Scheme 4). The possible linear product **24** was not detected or isolated from the reaction mixture. The ^1H NMR spectrum of the product in question showed two doublets for the benzene protons, in agreement with the angular[8] structure **25**.

Quinolinol **23** was then oxidized to the known[25] 8-(1-pyrrolidinyl)-5,6-quinolinedione (**26**). Treatment of quinone **26** with ylide **10a** afforded ethyl 3-oxo-6-(pyrrolidinyl)-3*H*-pyrano[3,2-*f*]quinoline-1-carboxylate (**27**) (73%).

From the above results, we conclude that treatment of a phenol with DMAD and PPh_3 can lead to the formation of a coumarin derivative, where the oxygen atom of the pyran ring belongs to the starting phenol, while the peri-selectivity in the construction of this new ring depends on the higher reactivity of the free *o*-positions of the phenol during the aromatic electrophilic substitution sequence. The previous transformation of the phenol to *o*-quinone, followed by treatment with an alkoxycarbonylmethylene(triphenyl)phosphorane can lead to the same coumarin, like above, or to its peri- or regio-isomer, depending on the position of the carbonyls in the *o*-quinone formed, and further on the electrophilicity of the carbon atoms of these two carbonyls during the initial olefination of one of them. More evidence is necessary in order to explain, why a γ-lactonization product, though in lower yield, is usually formed only in the second method from the common intermediates *o*-hydroxybutenedioates in both reactions. A possible explanation may be the difference in the configuration between these two intermediates.

3. Experimental

3.1. General

Mp's were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 1310 spectrophotometer as Nujol mulls. NMR spectra were recorded on a Bruker AM 300 (300 and 75 MHz for ^1H and ^{13}C, respectively) using $CDCl_3$ as solvent and TMS as an internal standard. *J* values are reported in hertz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under electron impact (EI) conditions or on a Perkin–Elmer API 100 Sciex simple quadrupole under electrospray ionization (ESI) conditions. Microanalyses were performed on a Perkin–Elmer 2400-II element analyzer. Silica gel no. 60, Merck A.G. has been used for column chromatography. Compounds **1**,[18] **9**,[21] **15**[22] and **26**[25] were prepared according to the literature.

3.1.1. Procedure for the synthesis of dimethyl 2-(4-hydroxy-2-methyl-3-quinolinyl)-2-butenedioate (7) and methyl 5-methyl-2-oxo-2*H*-pyrano[3,2-*c*]quinoline-4-carboxylate (8). 2-Methyl-4-hydroxyquinoline (**1**) (0.318 g, 2 mmol) and Ph_3P (0.524 g, 2 mmol) were dissolved in toluene (20 ml). A solution of DMAD (0.284 g, 0.246 ml, 2 mmol) in toluene (4 ml) was added dropwise over 16 min at −5 °C, and the orange solution was heated under reflux for 28 h. Evaporation of the solvent and separation by column chromatography (hexane/ethyl acetate 3:7) afforded **7** (0.391 g, 65%) and **8** (traces).

3.1.1.1. Dimethyl 2-(4-hydroxy-2-methyl-3-quinolinyl)-2-butenedioate (7). Yellow crystals, mp 236–238 °C (DCM); IR (Nujol) ν (cm^{-1}): 3446, 3105, 1728, 1632; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.27 (s, 3H), 3.62 (s, 3H), 3.72 (s, 3H), 7.14 (s, 1H), 7.26 (t, *J*=7.9 Hz, 1H), 7.32 (d, *J*=7.9 Hz, 1H), 7.49 (t, *J*=7.9 Hz, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 10.06 (s, 1H, exchanged by D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.1, 51.8, 52.8, 107.2, 108.8, 117.5, 123.7, 124.2, 125.9, 130.3, 131.8, 141.0, 147.6, 154.4, 165.1, 165.3; MS (EI) *m/z*: 301 (M^+, 6), 269 (4), 243 (15), 242 (100), 210 (13), 183 (19), 154 (55), 127 (12). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.68; H, 5.02; N, 4.52.

3.1.1.2. Methyl 5-methyl-2-oxo-2*H*-pyrano[3,2-*c*]quinoline-4-carboxylate (8). Yellow crystals, mp 176–

178 °C (dec) (DCM/hexane); IR (Nujol) ν (cm^{-1}): 3050, 1725, 1706, 1625; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.78 (s, 3H), 4.06 (s, 3H), 6.56 (s, 1H), 7.66 (t, J=8.9 Hz, 1H), 7.85 (t, J=8.9 Hz, 1H), 8.02 (d, J=8.9 Hz, 1H), 8.43 (d, J=8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.9, 53.0, 109.4, 110.6, 115.6, 116.3, 116.8, 125.8, 132.3, 140.8, 148.8, 154.4, 158.0, 160.9, 167.7; MS (EI) *m/z*: 269 (M^+, 100), 254 (7), 237 (49), 210 (63), 209 (35), 183 (31), 181 (16), 166 (9), 154 (29). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12; N, 5.20. Found: C, 66.71; H, 4.29; N, 5.04.

3.1.2. Procedure for the preparation of methyl 5-methyl-2-oxo-2*H*-pyrano[3,2-*c*]quinoline-4-carboxylate (8). Compound **7** (0.034 g, 0.113 mmol) (without solvent) was heated at 150–160 °C for 24 h. No reaction had happened as checked by TLC. The heating was continued for 4 days at 200–205 °C. Sublimation in the upper part of the apparatus gave compound **8** (0.003 g, 10%).

3.1.3. General procedure for the preparation of the quinolinols 11a–c and the azacoumarins 12a–c. A solution of hydroxyaldehyde **9** (2.7 mmol) and ylide **10a–c** (2.7 mmol) in dry toluene (50 ml) was heated at different temperatures under stirring and argon atmosphere. After cooling, quinolinols **11a**,**b** precipitated. The filtrate was evaporated in a rotary evaporator and the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:2) to give products **12a–c** and **11c**.

3.1.3.1. Ethyl 3-(4-hydroxy-2-methylquinolinyl)-2-propenoate (11a). Heating at 60 °C for 48 h. Yellow crystals (from DCM/hexane), mp 157–159 °C; yield 72%; IR (Nujol) ν (cm^{-1}): 3459, 3064, 1707, 1615; ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ: 1.31 (t, J=6.9 Hz, 3H), 2.63 (s, 3H), 4.21 (q, J=6.9 Hz, 2H), 7.33 (t, J=7.9 Hz, 1H), 7.48–7.62 (m, 3H), 7.74 (d, J=14.8 Hz, 1H), 8.26 (d, J=7.9 Hz, 1H), 11.70 (s, 1H, exchanged by D_2O); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz) δ: 13.8, 18.1, 59.0, 112.2, 117.3, 117.4, 123.3, 124.8, 125.3, 131.0, 136.9, 137.9, 148.4, 151.1, 168.2; MS (EI) *m/z*: 257 (M^+, 43), 212 (44), 211 (34), 184 (98), 183 (100), 154 (87), 128 (50), 127 (39). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.88; N, 5.45. Found: C, 70.19; H, 5.81; N, 5.17.

3.1.3.2. 5-Methyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (12a). Heating at 60 °C for 48 h. Yellow crystals (from DCM/hexane), mp 159–161 °C; yield 7%; IR (Nujol) ν (cm^{-1}): 3059, 1736, 1626; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.89 (s, 3H), 6.55 (d, J=9.8 Hz, 1H), 7.62 (t, J=7.9 Hz, 1H), 7.81 (t, J=7.9 Hz, 1H), 8.03 (d, J=7.9 Hz, 1H), 8.05 (d, J=9.8 Hz, 1H), 8.42 (d, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.5, 104.6, 116.3, 122.0, 126.9, 128.7, 132.0, 140.7, 148.6, 151.8, 152.6, 154.7, 160.6; MS (EI) *m/z*: 211 (M^+, 78), 183 (100), 154 (29), 128 (16), 127 (17), 102 (18), 77 (38), 76 (31). Anal. Calcd for $C_{13}H_9NO_2$: C, 73.91; H, 4.30; N, 6.63. Found: C, 73.81; H, 4.11; N, 6.53.

3.1.3.3. Ethyl 3-(4-hydroxy-2-methyl-3-quinolinyl)-2-methyl-2-propenoate (11b). Reflux for 11 days. Yellow crystals (from DCM), mp 199–201 °C; yield 76%; IR (Nujol) ν (cm^{-1}): 3434, 3062, 1702, 1635; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.33 (t, J=6.9 Hz, 3H), 2.35 (s, 3H), 2.83 (s, 3H), 4.23 (q, J=6.9 Hz, 2H), 7.29 (t, J=7.9 Hz, 1H), 7.47 (d, J=7.9 Hz, 1H), 7.56 (s, 1H), 7.57 (t, J=7.9 Hz, 1H), 8.28 (d, J=7.9 Hz, 1H), 11.34 (s, 1H, exchanged by D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.8, 14.6, 18.2, 59.9, 115.3, 117.0, 122.6, 124.1, 125.3, 130.4, 130.9, 133.9, 139.0, 146.7, 151.9, 167.7; MS (EI) *m/z*: 271 (M^+, 9), 226 (13), 199 (21), 198 (100), 183 (7), 159 (9), 130 (9), 102 (6). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.82; H, 6.32; N, 5.16. Found: C, 70.77; H, 6.33; N, 5.03.

3.1.3.4. 3,5-Dimethyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (12b). Reflux for 11 days. Yellow crystals (from DCM), mp 247–249 °C; yield 8%; IR (Nujol) ν (cm^{-1}): 3025, 1748, 1637, 1614; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.31 (s, 3H), 2.86 (s, 3H), 7.59 (t, J=7.9 Hz, 1H), 7.76 (t, J=7.9 Hz, 1H), 7.80 (s, 1H), 7.99 (d, J=7.9 Hz, 1H), 8.36 (d, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.5, 22.5, 110.2, 117.3, 121.6, 125.9, 126.7, 128.5, 131.2, 136.3, 145.0, 147.7, 155.6, 160.9; MS (EI) *m/z*: 225 (M^+, 100), 199 (11), 198 (21), 197 (44), 196 (59), 167 (21), 127 (9), 77 (21). Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.64; H, 4.93; N, 6.22. Found: C, 74.71; H, 5.23; N, 5.93.

3.1.3.5. Ethyl 2-benzyl-3-(4-hydroxy-2-methyl-3-quinolinyl)-2-propenoate (11c). Reflux for 6 days; eluting second from the column chromatography. Yellow crystals (from DCM), mp 231–233 °C; yield 17%; IR (Nujol) ν (cm^{-1}): 3467, 3102, 1700, 1626; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.16 (t, J=6.9 Hz, 3H), 2.30 (s, 3H), 3.66 (s, 2H), 4.11 (q, J=6.9 Hz, 2H), 7.02–7.16 (m, 5H), 7.34 (t, J=7.9 Hz, 2H), 7.55 (d, J=7.9 Hz, 1H), 7.57 (s, 1H), 8.38 (d, J=7.9 Hz, 1H), 9.24 (s, 1H, exchanged by D_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1, 19.4, 34.7, 60.7, 111.8, 116.3, 117.0, 121.4, 123.8, 125.7, 126.5, 128.0, 128.4, 132.0, 134.4, 139.8, 140.1, 143.7, 150.0, 164.7; MS (EI) *m/z*: 347 (M^+, 21), 301 (62), 273 (50), 256 (100), 228 (13), 196 (24), 91 (32), 77 (9). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.05; H, 6.10; N, 4.03. Found: C, 76.33; H, 6.00; N, 3.74.

3.1.3.6. 3-Benzyl-5-methyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (12c). Reflux for 6 days; eluting first from the column chromatography. Yellow crystals (from DCM), mp 163–165 °C; yield 7%; IR (Nujol) ν (cm^{-1}): 3058, 1724, 1634; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.75 (s, 3H), 3.96 (s, 2H), 7.26–7.48 (m, 5H), 7.57 (t, J=7.9 Hz, 1H), 7.61 (s, 1H), 7.74 (t, J=7.9 Hz, 1H), 7.98 (d, J=7.9 Hz, 1H), 8.35 (d, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.2, 36.9, 110.2, 117.2, 121.7, 126.8, 127.0, 128.4, 128.7, 128.9, 129.2, 131.4, 136.3, 137.2, 147.7, 155.7, 155.8, 160.3; MS (EI) *m/z*: 301 (M^+, 87), 300 (37), 287 (15), 273 (100), 244 (20), 202 (49), 196 (70), 167 (47), 105 (35), 91 (61), 77 (52). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.64. Found: C, 80.01; H, 5.05; N, 4.37.

3.1.4. Alternative procedure for the synthesis of ethyl 3-(4-hydroxy-2-methylquinolinyl)-2-propenoate (11a) and 5-methyl-2*H*-pyrano[3,2-*c*]quinolin-2-one (12a). A mixture of hydroxyaldehyde **9** (0.187 g, 1 mmol) and ylide **10a** (0.39 g, 1 mmol) in dry toluene (5 ml) in a conical flask was irradiated in a commercial microwave oven (800 W) for 3 min. The mixture, after the evaporation of the solvent, was separated by column chromatography (silica gel, ethyl acetate/hexane 7:3) to give compound **12a** (10 mg, 2%) and compound **11a** (0.11 g, 16%).

3.1.5. General procedure for cyclization of quinolinols 11a,b to azacoumarins 12a,b. Quinolinols **11a**,**b** (0.39 mmol) were heated without solvent in different temperatures and monitored by TLC. Sublimation in the upper part of the apparatus gave azacoumarins **12a**,**b**.

3.1.5.1. Synthesis of azacoumarin 12a. Heating for 66 h at 210–230 °C resulted to compound **12a** (30 mg, 37%).

3.1.5.2. Synthesis of azacoumarin 12b. Heating for 4 days at 180–185 °C gave compound **12b** (55 mg, 66%).

3.1.6. Procedure for the synthesis of methyl 6-methyl-2-oxo-2*H*-pyrano[3,2-*h*]quinolin-4-carboxylate (14). 5-Methyl-8-hydroxyquinoline (**13**) (0.105 g, 0.66 mmol) and Ph_3P (0.173 g, 0.66 mmol) were dissolved in toluene (7 ml). A solution of DMAD (0.094 g, 0.081 ml, 0.66 mmol) in toluene (2 ml) was added dropwise over 10 min at −5 °C, and the orange solution was heated under reflux for 5 h. Evaporation of the solvent and separation by column chromatography (hexane/ethyl acetate 1:2) afforded **14** (0.136 g, 76%) as yellow crystals, mp 233–235 °C (from ethyl acetate/hexane); IR (Nujol) ν (cm^{-1}): 3088, 1724, 1589; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.72 (s, 3H), 4.05 (s, 3H), 7.10 (s, 1H), 7.63 (dd, J_1=3.9 Hz, J_2=8.9 Hz, 1H), 8.15 (s, 1H), 8.36 (d, J=8.9 Hz, 1H), 9.11 (d, J=3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 18.7, 53.2, 119.0, 120.3, 122.3, 123.3, 129.6, 130.6, 132.4, 142.4, 150.7, 157.8, 160.9, 174.4; MS (EI) *m*/*z*: 269 (M^+, 93), 241 (91), 226 (18), 210 (100), 183 (92), 154 (92), 127 (45), 77 (38). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12; N, 5.20. Found: C, 67.19; H, 4.25; N, 5.12.

3.1.7. General procedure for the synthesis of benzofuranones 21a,b and pyridocoumarins 22a,b. A solution of quinone **15** (2 mmol) and ylide **16** or **10a** (4 mmol) in DCM (30 ml) was refluxed for 2 h. After evaporation of the solvent and separation by column chromatography (DCM/ethyl acetate 7:1) compounds **21a**,**b** and **22a**,**b** were obtained.

3.1.7.1. Methyl 2-[5-methyl-8-oxo-furo[2,3-*h*]quinolin-9(8*H*)-ylidene]acetate (21a). Yellow crystals (from DCM), mp 206–208 °C; yield 14%; IR (Nujol) ν (cm^{-1}): 3040, 1740, 1725, 1640, 1608; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.77 (s, 3H), 4.05 (s, 3H), 6.46 (s, 1H), 7.41 (s, 1H), 7.50 (dd, J_1=4.9 Hz, J_2=4.9 Hz, 1H), 8.35 (d, J=7.9 Hz, 1H), 8.89 (d, J=4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.1, 52.9, 111.7, 113.0, 118.2, 121.1, 122.7, 127.9, 132.7, 135.3, 146.0, 149.9, 150.0, 159.8, 166.7; MS (EI) *m*/*z*: 269 (M^+, 100), 241 (10), 211 (45), 210 (21), 183 (24), 181 (27), 154 (15). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12; N, 5.20. Found: C, 67.19; H, 4.37; N, 5.09.

3.1.7.2. Methyl 5-methyl-8-oxo-8*H*-pyrano[2,3-*h*]-quinoline-10-carboxylate (22a). Yellow crystals (from DCM), mp 200–202 °C (dec); yield 20%; IR (Nujol) ν (cm^{-1}): 3040, 1725, 1710, 1638, 1600; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.53 (s, 3H), 4.03 (s, 3H), 6.62 (s, 1H), 6.71 (s, 1H), 7.40 (t, J=6.9 Hz, 1H), 8.17 (d, J=6.9 Hz, 1H), 9.30 (d, J=6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.2, 53.2, 106.8, 110.0, 115.4, 127.9, 128.6, 129.9, 131.1, 134.6, 141.1, 145.4, 146.2, 160.8, 168.2; MS (EI) *m*/*z*: 269 (M^+, 100), 238 (20), 211 (50), 210 (23), 185 (33), 183 (80), 155 (17), 154 (54), 127 (10). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.90; H, 4.12; N, 5.20. Found: C, 67.13; H, 4.27; N, 5.18.

3.1.7.3. Ethyl 2-[5-methyl-8-oxo-furo[2,3-*h*]quinolin-9(8*H*)-ylidene]acetate (21b). Yellow crystals (from DCM), mp 286–288 °C; yield 22%; IR (Nujol) ν (cm^{-1}): 3050, 1740, 1715, 1640, 1605; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (t, J=6.9 Hz, 3H), 2.77 (s, 3H), 4.57 (q, J=6.9 Hz, 2H), 6.46 (s, 1H), 7.38 (s, 1H), 7.52 (dd, J_1=3.9 Hz, J_2=8.9 Hz, 1H), 8.36 (d, J=8.9 Hz, 1H), 8.88 (d, J=3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0, 19.1, 62.2, 110.6, 113.0, 118.2, 121.1, 124.7, 132.6, 141.1, 143.4, 147.0, 149.7, 155.7, 160.0, 166.9; MS (EI) *m*/*z*: 283 (M^+, 92), 255 (8), 238 (56), 211 (95), 183 (97), 154 (100), 127 (64), 101 (21). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.82; H, 4.63; N, 4.95. Found: C, 68.07; H, 4.71; N, 4.86.

3.1.7.4. Ethyl 5-methyl-8-oxo-8*H*-pyrano[2,3-*h*]quinoline-10-carboxylate (22b). Yellow crystals (from DCM), mp 178–180 °C; yield 47%; IR (Nujol) ν (cm^{-1}): 3040, 1720, 1680, 1630, 1605; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.42 (t, J=6.9 Hz, 3H), 2.50 (s, 3H), 4.50 (q, J=6.9 Hz, 2H), 6.56 (s, 1H), 6.67 (s, 1H), 7.36 (t, J=6.9 Hz, 1H), 8.14 (d, J=6.9 Hz, 1H), 9.27 (d, J=6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9, 19.1, 62.3, 106.6, 109.9, 115.5, 127.9, 129.8, 131.0, 134.6, 139.6, 141.8, 145.7, 158.1, 160.9, 167.6; MS (EI) *m*/*z*: 283 (M^+, 67), 255 (5), 238 (41), 227 (5), 211 (100), 183 (70), 154 (69), 127 (13). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.82; H, 4.63; N, 4.95. Found: C, 68.13; H, 4.69; N, 4.73.

3.1.8. Procedure for the synthesis of methyl 3-oxo-3*H*-pyrano[3,2-*f*]quinoline-1-carboxylate (25). 6-Quinolinol (**23**) (0.435 g, 3 mmol) and Ph_3P (0.786 g, 3 mmol) were dissolved in toluene (30 ml). A solution of DMAD (0.426 g, 0.369 ml, 3 mmol) in toluene (6 ml) was added dropwise over 15 min at −5 °C, and the orange solution was then refluxed for 5 h. Evaporation of the solvent and separation by column chromatography (hexane/ethyl acetate 1:1) afforded **25** (0.711 g, 93%) as yellow crystals, mp 168–169 °C (from ethyl acetate); IR (Nujol) ν (cm^{-1}): 3020, 1730, 1710, 1630, 1600, 1495; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.08 (s, 3H), 6.68 (s, 1H), 7.52 (dd, J_1=4.0 Hz, J_2=7.9 Hz, 1H), 7.73 (d, J=9.8 Hz, 1H), 8.14 (d, J=7.9 Hz, 1H), 8.34 (d, J=9.8 Hz, 1H), 8.97 (d, J=4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 53.7, 109.8, 116.8, 121.2, 122.1, 123.6, 131.8, 135.5, 144.8, 145.5, 149.6, 154.6, 158.9, 167.1; MS (ESI): *m*/*z* for $[M+H]^+$ 256. Anal. Calcd for $C_{14}H_9NO_4$: C, 65.87; H, 3.56; N, 5.49. Found: C, 66.14; H, 3.69; N, 5.35.

3.1.9. Procedure for the synthesis of ethyl 3-oxo-6-(pyrrolidinyl)-3*H*-pyrano[3,2-*f*]quinoline-1-carboxylate (27). A solution of quinone **26** (0.684 g, 3 mmol) and ylide **10a** (2.088 g, 6 mmol) in DCM (15 ml) was refluxed for 2 h. After evaporation of the solvent and separation by column chromatography (hexane/ethyl acetate 2:1) compound **27** (0.713 g, 73%) was received as yellow crystals (from DCM/hexane), mp 149–151 °C; IR (Nujol) ν (cm^{-1}): 3045, 1720, 1708, 1635, 1590, 1500; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.39 (t, J=7.8 Hz, 3H), 2.03–2.05 (m, 4H), 3.80–3.91 (m, 4H), 4.49 (q, J=7.8 Hz, 2H), 6.16 (s, 1H),

6.56 (s, 1H), 7.36 (dd, J_1=2.9 Hz, J_2=7.9 Hz, 1H), 7.99 (d, J=7.9 Hz, 1H), 8.71 (d, J=2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.9, 25.7, 52.5, 62.7, 98.5, 107.7, 110.9, 121.5, 125.3, 131.4, 139.3, 144.9, 145.6, 150.4, 157.5, 160.9, 167.9; MS (ESI): *m/z* for $[M+H]^+$ 339. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.43; H, 5.37; N, 8.28. Found: C, 67.49; H, 5.53; N, 8.20.

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