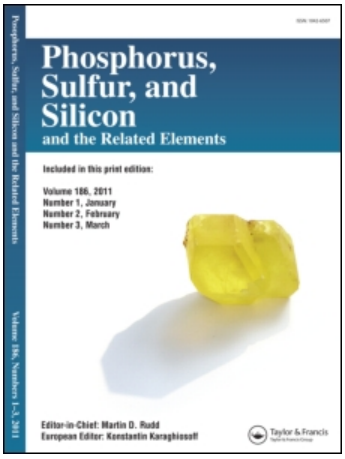

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Triphenylphosphine-Mediated Synthesis of the *E/Z* Isomers of Methyl 6-(1,2-Di(methoxycarbonyl))-8-(ethyl Carbamoylformyl)-2-oxo-2*H*-chromene-4-carboxylate

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Triphenylphosphine-mediated reaction of dimethyl acetylenedicarboxylate with ethyl (2-hydroxyphenylcarbamoyl)formate in boiling toluene produces a mixture of methyl 8-(ethyl carbamylformyl)-2-oxo-2H-chromene-4-carboxylate and the E/Z isomers of methyl 6-(1,2-di(methoxycarbonyl)-8-(ethyl carbamoylformyl)-2-oxo-2H-chromene-4-carboxylate in moderate yields.

Keywords 2-oxo-2*H*-chromene; acetylenic ester; aromatic substitution; triphenylphosphine

INTRODUCTION

2-Oxo-2*H*-chromenes (coumarines) and their derivatives have stimulated interesting research in organic chemistry and medicine due to their antibiotic,[1] anticoagulant,[2,3] and antiinflamatory[4] properties. Also a considerable number of natural or synthetic derivatives of coumarine have found pharmaceutical applications.[5,6] Thus, the synthesis of this heterocyclic nucleus is of interest. Coumarines have been synthesized by several methods.[7,8] Recently, we reported[9] a new method for the synthesis of 3-pyrrolin-2-ones **2** by an intramolecular Wittig reaction[10] of phosphorane **1** (Scheme 1). In order to prepare 3-pyrrolin-2-ones with a hydroxyl group in the *ortho* position of

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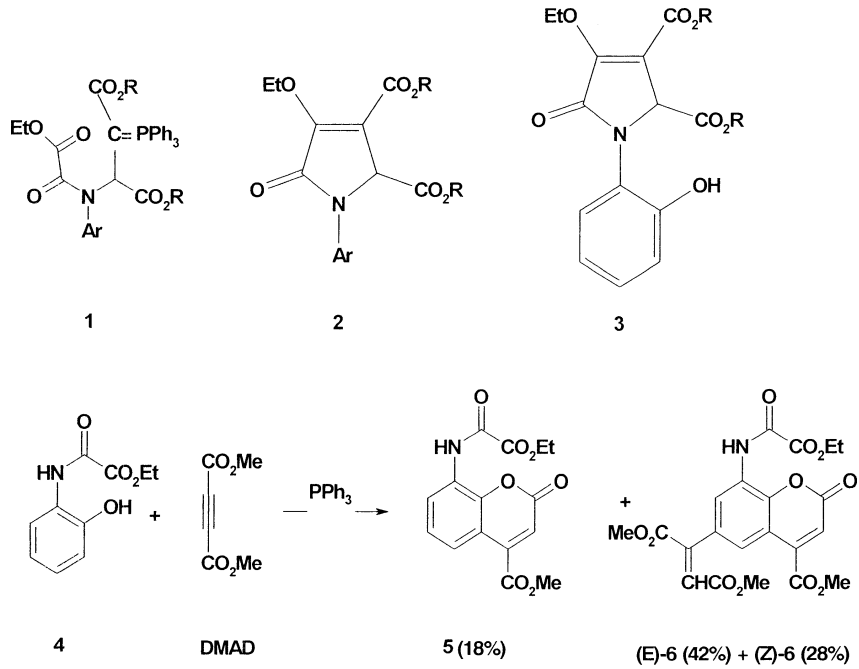
the aromatic moiety, such as **3**, we attempted the reaction of ethyl (2-hydroxyphenylcarbamoyl)formate (**4**) with dimethyl acetylendicarboxylate (DMAD) in the presence of triphenylphosphine in boiling toluene. The reaction proceeded spontaneously, but instead of **3**, a mixture of **5** and the *E*/*Z* isomers of **6** were obtained in moderate yields (Scheme 1). The reaction of tertiary phosphorus nucleophiles with DMAD and phenol have been discussed with emphesis upon the synthesis of phosphorus heterocycles.[11]



SCHEME 1

RESULTS AND DISCUSSION

The reaction of **4** with DMAD in the presence of triphenylphosphine was carried out in toluene at a reflux temperature for 8 h. The solvent was removed, and the yellow solid was separated by preparative TLC to afford methyl 8-(ethyl carbamylformyl)-2-oxo-2*H*-chromene-4-carboxylate (**5**) and the *E*/*Z* isomers of methyl 6-(1,2-di(methoxycarbonyl)-8-(ethyl carbamoylformyl)-2-oxo-2*H*-chromene-4-carboxylate (**6**). The structures of compounds **5** and **6** were assigned on the basis of their elemental analyses and their IR,^{1}H NMR, ^{13}C

NMR, and mass spectral data. The mass spectra of these compounds display molecular ion peaks at appropriate m/z values. Any initial fragmentation involved the loss of ester moieties and the scission of the heterocyclic ring.

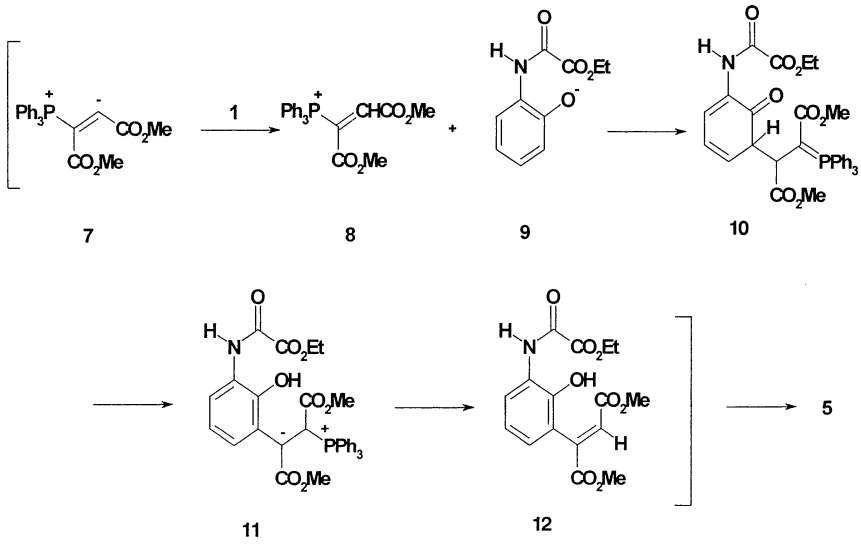
The ^{1}H NMR spectrum of **5** exhibited signals for methyl ($\delta = 1.47$ ppm), methoxy ($\delta = 4.04$ ppm), and methylene ($\delta = 4.48$ ppm) protons together with characteristic multiplets ($\delta = 7.01$–8.70 ppm) for the aromatic protons. The amidic proton signal appears at $\delta = 9.50$ ppm. The ^{13}C NMR spectrum of **5** showed 15 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section. The ^{1}H and ^{13}C NMR spectra of **6** are fairly similar to those of **5** except for the side chain and the protons of the aromatic ring, which exhibit characteristic signals with appropriate chemical shifts (see the Experimental section). The structural assignments of compounds **5** and **6** made on the basis of their ^{1}H and ^{13}C NMR spectra were supported by their IR spectra. The carbonyl region of these compounds displayed characteristic absorption bands. The assignment of configuration of the carbon–carbon double bound in **6** is based on the chemical shift of the olefinic proton.[12]

A plausible mechanism for the formation of coumarine derivative **5** is shown in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[13,14] it is reasonable to assume that compound **5** results from the initial addition of triphenylphosphine to DMAD and subsequent protonation of the reactive 1:1 adduct by **3**. Then the positively charged ion **8** is attacked by the conjugate base of **4**. The product is presumably produced by the intramolecular lactonization of the vinyl substituted phenol **12**. Similar pathways may be proposed for the formation of compound **6**. The E/Z isomers of **6** are presumably formed via further vinylation of **5** by the electrophilic substitution reaction with **8**.

We have found a simple reaction for the synthesis of methyl 8-(ethyl carbamylformyl)-2-oxo-2*H*-chromene-4-carboxylate (**5**) and the E/Z isomers of methyl 6-(1,2-di(methoxycarbonyl)-8-(ethyl carbamoylformyl)-2-oxo-2*H*-chromene-4-carboxylate (**6**) in moderate yields. The one-pot nature of the procedure makes it an acceptable method for preparation of substituted coumarines.

EXPERIMENTAL

Ethyl (2-hydroxyphenylcarbamoyl)formate (**4**) was prepared using 2-aminophenol and ethyl chloro-oxalate. Triphenylphosphine and DMAD were obtained from Fluka and were used without further purification. Melting points were measured on Electrothermal 9100 apparatus.



SCHEME 2

Elemental analyses for C and H were performed using a Heraus CHN-O-Rapid analyzer. The NMR spectra were recorded at 300 (^{1}H) and 75.5 (^{13}C) MHz on a Bruker 300-AVANCE FT-NMR instrument with $CDCl_3$ as a solvent. Chemical shifts (δ) are reported relative to TMS as the internal standard. IR spectra were recorded on a Bomem MB-100 IR spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Preparative TLC was performed on glass plates prepared with silica gel. Column chromatography was performed using 230–400 mesh Merck silica gel, and mixtures of *n*-hexane and EtOAc were used as an eluent.

Preparation of Compounds 5 and 6

To a magnetically stirred solution of **4** (1.05 g, 5 mmol) and triphenylphosphine (1.31 g, 5 mmol) in toluene (35 mL) a mixture of DMAD (1.42 g, 10 mmol) in toluene (5 mL) at room temperature was added dropwise. The mixture was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was purified by TLC using *n*-hexane and EtOAc as an eluent. The light yellow crystals of **5** were separated from the E/Z mixture of **6**. The isomeric mixture of **6** was separated by preparative TLC.

Methyl 8-(Ethyl Carbamylformyl)-2-Oxo-2*H*-Chromene-4-Carboxylate (5)

Light yellow crystals; yield: 0.27 g (18%), m.p. 216–218 °C. IR (KBr): 3386 (NH), 1745 and 1725 (C=O), 1271 (C—O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (t, 3 H, $^3J_{HH} = 7.2$ Hz, CH_3), 4.04 (s, 3 H, OCH_3), 4.48 (q, 2 H, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.01 (s, 1 H, CH), 7.39 (t, 1 H, J_{HH} = 8.2 Hz, CH), 8.09 (dd, 1H , $^3J_{HH} = 8.2$ Hz and $^4J_{HH} = 2.0$ Hz, CH), 8.70 (dd, 1 H, $^3J_{HH} = 8.2$ Hz and $^4J_{HH} = 2.0$ Hz, CH), 9.50 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$):$\delta = 14.4$ (CH_3), 53.8 (OCH_3), 64.4 (OCH_2), 116.2 (C), 119.8 (CH), 123.2 (CH), 123.3 (C), 123.4 CH), 125.3 (CH), 143.1 (C), 144.0 (C), 154.7 (C=O), 158.5 (C=O), 160.4 (C=O), 164.3 (C=O) ppm. MS (EI, 70 eV): m/z = 319 (M^+, 7), 304 (32), 290 (65), 260 (43), 246 (57), 228 (11), 105 (100). Anal. calcd. for $C_{15}H_{13}NO_7$ (319.3): C, 56.43; H, 4.10; N, 4.39. Found: C, 56.58; H, 4.08; N, 4.41%.

Methyl (*Z*)-6-(1,2-Di(methoxycarbonyl)-8-(ethyl Carbamoylformyl)-2-oxo-2*H*-chromene-4-carboxylate (*Z*-6)

Yellow crystals; yield: 0.64 g (28%), m.p. 132–134°C, IR (KBr): 3383 (NH), 1735, 1731, and 1720 (C=O), 1271 and 1197 (C—O) cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): $\delta = 1.44$ (t, 3 H, $^3J_{HH} = 7.2$ Hz, CH_3), 3.80 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.46 (q, 2 H, $^3J_{HH} = 7.2$ Hz, OCH_2) , 6.44 (s, 1 H, CH), 7.09 (s, 1 H, CH), 8.33 (d, 1 H, $^4J_{HH} = 2.1$ Hz, CH), 8.92 (d, 1 H, $^4J_{HH} = 2.1$ Hz, CH), 9.56 (s, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.4$ (CH_3), 52.6 (OCH_3), 53.3 (OCH_3), 53.9 (OCH_3), 64.5 (OCH_2), 116.5 (C), 119.2 (CH), 120.8 (C), 121.0 (CH), 121.9 (CH), 126.0 (CH), 130.5 (C), 142.0 (C), 144.8 (C), 147.1 (C), 154.8 (C=O), 157.7 (C=O), 160.2 (C=O), 163.7 (C=O), 165.4 (C=O), 168.0 (C=O) ppm. MS (EI, 70 eV): m/z = 461 (M^+, 4), 446 (53), 432 (31), 402 (52), 319 (28), 290 (46), 260 (49), 246 (63), 228 (31), 105 (100). Anal. calcd for $C_{21}H_{19}NO_{11}$ (461.3): C, 54.67; H, 4.15; N, 3.04. Found: C, 54.90; H, 4.12; N, 3.08%.

Methyl (*E*)-6-(1,2-Di(methoxycarbonyl)-8-(ethyl Carbamoylformyl)-2-oxo-2*H*-chromene-4-carboxylate (*E*-6)

Yellow crystals; yield: 0.96 g (42%), m.p. 138–140°C. IR (KBr): 3383 (NH), 1734, 1728, and 1722 (C=O), 1225, 1221, and 1218 (C—O) cm^{-1}. ^1H NMR (300.1 MHz, $CDCl_3$): $\delta = 1.45$ (t, 3 H, $^3J_{HH} = 7.2$ Hz, CH_3), 3.68 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.48 (q, 2 H, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.05 (s, 1 H, CH), 7.15 (s, 1 H, CH), 8.05 (d, 1 H, $^4J_{HH} = 2.1$ Hz, CH), 8.68 (d, 1 H, $^4J_{HH} = 2.1$ Hz, CH), 9.59 (s,

1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.5$ (CH_3), 52.5 (OCH_3), 53.6 (OCH_3), 53.7 (OCH_3), 64.4 (OCH_2), 115.7 (C), 120.3 (CH), 123.8 (C), 124.0 (CH), 125.0 (C), 130.4 (CH), 131.0 (C), 142.6 (C), 143.1 (C), 147.1 (C), 154.6 (C=O), 158.2 (C=O), 160.3 (C=O), 164.0 (C=O), 165.4 (C=O), 166.3 (C=O) ppm. MS (EI, 70 eV): m/z = 461 (M^+, 3), 446 (48), 432 (39), 402 (48), 319 (21), 290 (43), 260 (38), 246 (53), 228 (20), 105 (100). Anal. calcd for $C_{21}H_{19}NO_{11}$ (461.3): C, 54.67; H, 4.15; N, 3.04. Found: C, 54.86; H, 4.10; N, 3.10%.

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