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Vinylphosphonium Salt Mediated Facile Synthesis of Trialkyl 4-(2-Quinolyl)-1-cyclobutene-1,2,3-tricarboxylates and Dialkyl 3-Ethoxy-4-oxo-5-(2-(1*H*)-quinolinylidene)-2-cyclopentene-1,2-dicarboxylates

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Summary. The reactive 1:1 intermediate produced in the reaction between dialkyl acetylenedicarboxylates and triphenylphosphine was trapped by ethyl 3-(1,2-dihydroquinoline-2-ylidene)-pyruvate to yield the isomeric dialkyl 3-ethoxy-4-oxo-5-(2-(1*H*)-quinolinylidene)-2-cyclopentene-1,2-dicarboxylates and trialkyl 4-(2-quinolyl)-1-cyclobutene-1,2,3-tricarboxylates in nearly 4:1 ratio.

Keywords. Quinolines; Cyclobutenes; Cyclopentenones; Triphenylphosphine; Acetylenic esters.

Introduction

Quinoline and its derivatives continue to capture the attention of synthetic organic chemists, and a large number of quinoline ring syntheses and applications of known methods to new problems in quinoline chemistry have been reported [1–3]. 2-Substituted quinolines are incorporated in many biologically active compounds and natural products. Numerous natural products, including prominent alkaloids such as quinine, belong to the group of quinoline alkaloids [1–3]. Quinoline derivatives with a carbocyclic ring system in position 2 are particularly suitable building blocks for natural product synthesis.

As part of our current studies on the development of new routes in heterocyclic and carbocyclic synthesis [4–6], we report a facile synthesis of the functionalized quinolines **2** and **3** *via* an intramolecular *Wittig* reaction [7, 8].

Results and Discussion

The reaction of triphenylphosphine with dialkyl acetylenedicarboxylates **1** in the presence of a strong NH-acid such as ethyl 3-(1,2-dihydroquinoline-2-ylidene)-

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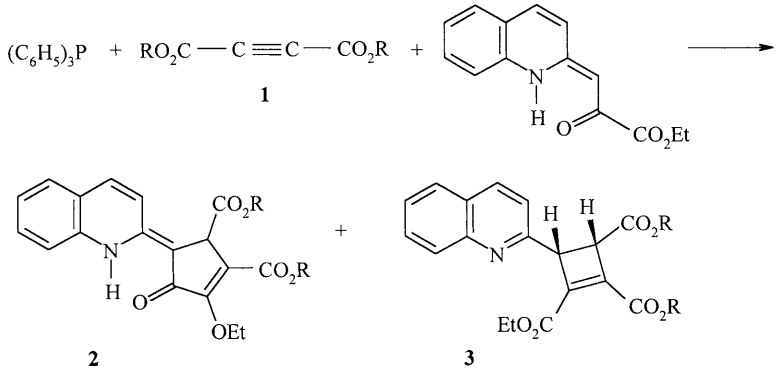
pyruvate afforded the isomeric dialkyl 3-ethoxy-4-oxo-5-(2(1*H*)-quinolinylidene)-2-cyclopentene-1,2-dicarboxylates (**2**) and trialkyl 4-(2-quinolyl)-1-cyclobutene-1,2,3-tricarboxylates (**3**) in nearly 4:1 ratio and good yields (Scheme 1). The structures of **2** and **3** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectra. The mass spectra of the isomeric compounds are fairly similar and display molecular ion peaks at $m/z = 360$ and 397. Any initial fragmentation involves the loss of the ester moieties. The ^{1}H NMR spectrum of **2a** exhibits three single sharp lines, readily recognizable as arising from methoxy ($\delta = 3.64$ and 3.78 ppm) and methine ($\delta = 4.34$ ppm) protons, along with characteristic multiplets for the ethoxy group. The protons of the quinoline residue appear as a fairly complex multiplet in the aromatic region. The NH group exhibits a broad line at $\delta = 14.54$ ppm, indicating intramolecular hydrogen bonding with the vicinal carbonyl group.

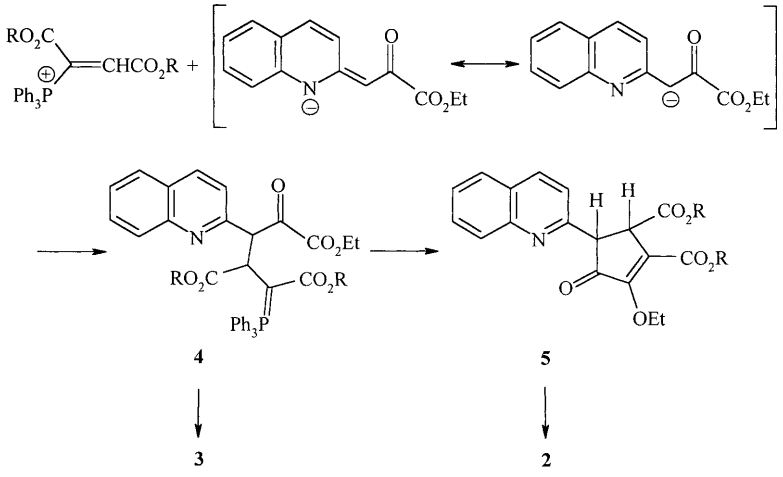
The ^{1}H NMR spectra of the cyclobutene derivatives **3a** and **3b** display signals at about $\delta = 4.14$–4.17 and $4.74-4.50$ ppm for the two methine groups (doublets, $^3J_{HH} = 5.1-5.7$ Hz), in agreement with the *cis* geometry of these protons [9]. The ^{13}C NMR spectra of **3a** and **3b** exhibit two signals at about $\delta = 45-47$ ppm for the two CH groups. A partial assignment of the ^{13}C signals of **2** and **3** is given in the Experimental.

Although we have not yet established the mechanism of the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of ethyl 3-(1,2-dihydroquinoline-2-ylidene)-pyruvate in an experimental manner, a possible explanation is proposed in Scheme 2 on the basis of the well-established chemistry of trivalent phosphorus nucleophiles [10–14]. It is reasonable to assume that **2** and **3** result from an initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by ethyl 3-(1,2-dihydroquinoline-2-ylidene)-pyruvate. Then, the positively charged ion might be attacked by the



1, 2, 3	*R*	Yield of 2 + 3	2:3
a	Me	94%	4.2:1
b	Et	87%	3.8:1

Scheme 1



Scheme 2

conjugate base of the NH-acid to form the phosphorane **4**, which is converted to quinoline derivatives **3** and **5**. Compound **5** apparently isomerizes under the reaction conditions employed to produce the cyclopentenone ring system **2** (see Scheme 2).

In summary, the presented method carries the advantage of being performed under neutral conditions and requiring no activation or modification of the educts. Its one-pot nature makes it an interesting alternative to multistep approaches [1, 3].

Experimental

Acetylenic esters and triphenylphosphine were obtained from Fluka and were used without further purification. Ethyl 3-(1,2-dihydroquinoline-2-ylidene)-pyruvate was prepared by known methods [15, 16]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were measured with a Bruker DRX-500 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70–230 mesh.

General procedure (exemplified on **2a** *and* **3a***)*

To a magnetically stirred solution of 0.524 g triphenylphosphine (2 mmol) and 0.486 g ethyl 3-(1,2-dihydroquinoline-2-ylidene)-pyruvate (2 mmol) in 4 cm^3 CH_2Cl_2, a mixture of 0.284 g dimethyl acetylenedicarboxylate (2 mmol) in 2 cm^3 CH_2Cl_2 was added dropwise at −5°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed under reduced pressure, and the solid residue was washed with 2 × 10 cm^3 cold Et_2O; the product was obtained as a yellow powder. The ^{1}H NMR spectrum of the crude product was consistent with the presence of a nearly 4:1 mixture of two isomeric products (see below).

The solid residue was separated by silica column chromatography (Merck 230–400 mesh) using hexane-ethyl acetate as eluent. The first compound was eluted using a 3:1 mixture and identified as **3a**. Elution with a 2:1 mixture gave **2a**.

Dimethyl 3-ethoxy-4-oxo-5-(2(1H)-quinolinylidene)-2-cyclopentene-1,2-dicarboxy-late (**2a**; $C_{20}H_{19}NO_6$)

Orange crystals; m.p.: 189–190°C (hexane: ethyl acetate = 1:1); yield: 0.55 g (76%); IR (KBr): $\nu = 1725, 1679, 1630$ (C=O) cm^{-1}; MS: *m/z* (%) = 360 (M^+, 2), 311 (8), 280 (28), 250 (96), 222 (65), 194 (47), 166 (100), 140 (97), 128 (77), 59 (22); ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.44 (3H, t, $J = 7$ Hz, CH_3), 3.64 and 3.78 (6H, 2s, $2OCH_3$), 4.34 (1H, s, CH), 4.87 (2H, q, $J = 7$ Hz, OCH_2), 7.27 (1H, t, $J = 7$ Hz, CH), 7.29 (1H, d, $J = 9.5$ Hz, CH), 7.40 (1H, d, $J = 8$ Hz, CH), 7.53 (1H, d, $J = 8$ Hz, CH), 7.55 (1H, t, $J = 8$ Hz, CH), 7.78 (1H, d, $J = 9.5$ Hz, CH), 14.54 (1H, br s, N-H $\cdots$ O=C) ppm; ^{13}C NMR (125 MHz, δ, $CDCl_3$): 16.39 (OCH_2CH_3), 46.05 (CH), 51.96 and 52.76 ($2OCH_3$), 68.02 (OCH_2CH_3), 100.23 and 116.14 (2C), 117.59 and 118.68 (2CH), 123.41 (C), 124.71, 128.39, 132.29 and 137.28 (4CH), 138.81 and 148.82 (2C), 163.92, 164.64 and 172.97 (C=*C*-O and 2C=O, ester), 183.63 (C=O) ppm.

1-Ethyl 2,3-dimethyl (+/−)-4-(2-quinolyl)-1-cyclobutene-1,2,3-tricarboxylate (**3a**; $C_{20}H_{19}NO_6$)

Colorless crystals; m.p.: 143–144°C (hexane: ethyl acetate = 1:1); yield: 0.13 g (18%); IR (KBr): $\nu = 1745, 1701$ (shoulder, C=O), 1630 (C=C) cm^{-1}; MS: *m/z* (%) = 360 (M^+, 1), 311 (10), 250 (76), 222 (70), 140 (100), 128 (70), 59 (18); ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.37 (3H, t, $J = 7$ Hz, CH_3), 3.69 and 3.74 (6H, 2s, $2OCH_3$), 4.17 (1H, d, $J = 5.7$ Hz, CH), 4.35 (2H, 2 dq, AMX_3 system, $^2J_{HH} = 10.9$ Hz, $^3J_{HH} = 7$ Hz, OCH_2), 4.50 (1H, d, $J = 5.7$ Hz, CH), 7.57 (1H, t, $J = 7$ Hz, CH), 7.70 (1H, t, $J = 7.3$ Hz, CH), 7.82 (1H, d, $J = 8.1$ Hz, CH), 8.04 (1H, d, $J = 8.4$ Hz, CH), 8.20 (1H, d, $J = 8.6$ Hz, CH), 8.71 (1H, d, $J = 8.6$ Hz, CH) ppm; ^{13}C NMR (125 MHz, δ, $CDCl_3$): 14.73 (CH_3), 45.15 and 46.38 (CH-CH), 52.89 and 52.92 ($2OCH_3$), 61.63 (OCH_2CH_3), 122.85, 127.98, 128.28, 128.63, 130.20 and 130.61 (6CH), 131.69, 136.77, 148.11, 149.46 and 153.82 (5C), 162.00, 170.51 and 170.82 (3C=O) ppm.

Diethyl 3-ethoxy-4-oxo-5-(2(1H)-quinolinylidene)-2-cyclopentene-1,2-dicarboxylate (**2b**; $C_{22}H_{23}NO_6$)

Orange crystals; m.p.: 148–150°C (hexane: ethyl acetate = 1:1); yield: 0.55 g (69%); IR (KBr): $\nu = 1716, 1670, 1629$ (C=O) cm^{-1}; MS: *m/z* (%) = 397 (M^+, 3), 266 (11), 251 (73), 194 (30), 166 (64), 128 (44), 87 (100); ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.18, 1.31 and 1.44 (9H, t, $J = 7.1$ Hz, $3CH_3$), 4.11 (2H, 2dq, $^2J_{HH} = 10.8$ Hz, $^3J_{HH} = 7.1$ Hz, AMX_3 system, OCH_2), 4.23 (2H, m, ABX_3 system, OCH_2), 4.35 (1H, s, CH), 4.84 (2H, m, ABX_3 system, OCH_2), 7.28 (1H, t, $J = 7$ Hz, CH), 7.34 (1H, d, $J = 9.3$ Hz, CH), 7.43 (1H, t, $J = 7$ Hz, CH), 7.55 (1H, d, $J = 9$ Hz, CH), 7.57 (1H, d, $J = 8$ Hz, CH), 7.79 (1H, d, $J = 8.1$ Hz, CH), 14.65 (1H, br s, N-H $\cdots$ O=C) ppm; ^{13}C NMR (125 MHz, δ, $CDCl_3$): 14.53, 14.66 and 16.30 ($3CH_3$), 46.37 (CH), 60.68, 61.56 and 68.16 ($3OCH_2$), 100.00 and 116.68 (2C), 117.67 and 118.93 (2CH), 123.46 (C), 124.72, 128.37, 132.31 and 137.38 (4CH), 138.69 and 148.84 (2C), 163.88, 164 and 172.43 (C=*C*-O and 2C=O, ester), 183.81 (C=O) ppm.

Triethyl (+/−)-4-(2-quinolyl)-1-cyclobutene-1,2,3-tricarboxylate (**3b**; $C_{22}H_{23}NO_6$)

Colorless crystals; m.p.: 112–114°C (hexane: ethyl acetate = 1:1); yield: 0.14 g (18%); IR (KBr): $\nu = 1740, 1701$ (C=O), 1629 (C=C) cm^{-1}; MS: *m/z* (%) = 397 (M^+, 2), 325 (5), 251 (100), 194 (42), 166 (68), 87 (52); ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.19 (3H, t, $J = 7.1$ Hz, CH_3), 1.27 (3H, t, $J = 7$ Hz, CH_3), 1.37 (3H, t, $J = 7.1$ Hz, CH_3), 4.14 (1H, d, $J = 5.1$ Hz, CH), 4.10–4.25 (4H, m, $2ABX_3$ system, $2OCH_2$), 4.34 (2H, 2dq, $^2J_{HH} = 10.8$ Hz, $^3J_{HH} = 7.1$ Hz, AMX_3 system, OCH_2), 4.47 (1H, d, $J = 5.1$ Hz, CH), 7.55 (1H, t, $J = 7.2$ Hz, CH), 7.69 (1H, t, $J = 7.2$ Hz, CH), 7.80 (1H, d,

$J = 8.1$ Hz, CH), 8.04 (1H, d, $J = 8.1$ Hz, CH), 8.18 (1H, d, $J = 8.6$ Hz, CH), 8.69 (1H, d, $J = 8.6$ Hz, CH) ppm; ^{13}C NMR (125 MHz, δ, $CDCl_3$): 14.56, 14.58 and 14.64 ($3CH_3$), 45.33 and 46.63 (CH-CH), 61.20, 61.41 and 61.51 ($3OCH_2$), 122.81, 127.89, 128.13, 128.61, 130.15 and 130.33 (6CH), 132.1, 136.74, 148.02, 149.59 and 153.68 (5C), 161.98, 169.72 and 169.94 (3C=O) ppm.

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