One-step Synthesis of Dialkyl 1,2-Dihydroquinoline-2,3-dicarboxylates. A Vinyltriphenylphosphonium Salt Mediated Intramolecular Wittig Reaction†

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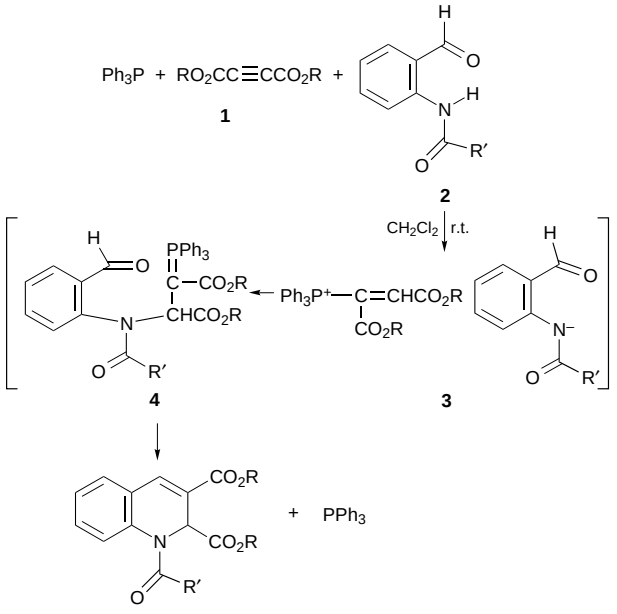
Dialkyl 1,2-dihydroquinoline-2,3-dicarboxylates are formed in a one-pot reaction from amide derivatives of 2-aminobenzaldehyde, dialkyl acetylenedicarboxylates and triphenylphosphine in CH_2Cl_2 in high yields.

Quinolines[1] are interesting synthetic targets because they act as building blocks for a large number of natural products. In recent years there has been an increase in interest in the synthesis of quinoline compounds. This interest has resulted from the use of such compounds in a variety of biological and synthetic applications.[2] While a number of synthetic methodologies for the quinoline ring system have been developed,[3] the literature describing a novel one-pot cyclization method based on consecutive processes is rather scarce. Recently, we have established a heterocyclic synthesis using a novel approach to vinylphosphonium salts.[4,5] Here we describe a facile one-pot synthesis of dialkyl 1,2-dihydroquinoline-2,3-dicarboxylates (**5**) in high yields.



Several examples are known in which an unsaturated heterocyclic compound is formed from a phosphorane connected to a carbonyl group by a chain containing a heteroatom.[6–10] Thus, quinoline **5** may be considered as the product of an intramolecular Wittig reaction. Such addition-cyclization products apparently result from the initial addition of triphenylphosphine to the acetylenic ester[11,12] and concomitant protonation of the 1:1 adduct, followed by attack of the anion of the 2-aminobenzaldehyde derivative on the vinylphosphonium cation to form the phosphorane **4** which is then converted into quinolines.

The essential structures of compounds **5a–f** were deduced from their elemental analyses and their ^{1}H and ^{13}C NMR spectra. The molecular ion peak is very weak in the mass spectra of **5a–f** accompanied by a stronger M + 1 peak owing to the protonation of these molecules in the mass spectrometer. Initial fragmentations involve loss from one of the quinoline side chains.

The ^{1}H NMR spectrum of **5a** displayed five single lines readily recognizable as arising from methyl (δ 2.32), methoxy (δ 3.61 and 3.88), N—CH (δ 6.62) and olefinic CH (δ 7.61) protons, along with a fairly complex multiplet in the aromatic region (see Experimental section). The noise-decoupled ^{13}C NMR spectrum of **5a** showed 15 distinct resonances in agreement with the dihydroquinoline structure. Partial assignments of these resonances are given in the Experimental section.

The ^{1}H and ^{13}C NMR spectra of **5b–f** are similar to those of **5a**, except for the ester groups and the amide moiety, which exhibit characteristic signals with appropriate chemical shifts (see Experimental section).

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **5a–f** were supported by measurement of their IR spectra. The carbonyl region of the spectrum exhibited three distinct absorption bands for each compound (see Experimental section). Of special interest is the ester absorption at 1691–1714 cm^{-1} for these compounds. Conjugation with the carbon–carbon double bond appears to be a plausible factor in the reduction of these bands.[13]

In conclusion, vinyltriphenylphosphonium salts have been shown to be useful precursors for a new and efficient synthetic route to 1,2-dihydroquinoline derivatives. The one-pot nature of the present procedure makes it an alternative to multistep approaches.[14–16] Further applications of this type of addition-cyclization to the synthesis of interesting heterocycles will be reported in due course.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-rapid analyser. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Preparation of Anilides **2a** *and* **2d**.—Compounds **2a** and **2d** were prepared by known methods[17] and identified as follows. 2′-Formylacetanilide **2a**: white crystals, mp 68–69 °C. δ_H ($CDCl_3$) 2.23 (3 H, s, CH_3CON), 7.1–7.7 (3 H, m, arom.), 8.71 (1 H, d, *J* 8.1 Hz, 3-H), 9.88 (1 H, s, CHO), 11.1 (1 H, brs, CONH). δ_C ($CDCl_3$) 25.00 (CH_3), 119.35, 122.49, 135.71 and 135.73 (4 CH), 121.27 (C2), 140.61 (C1), 169.07 (CON), 195.22 (CHO). 2′-Formylbenzanilide **2d**: white crystals, mp 70–71 °C. δ_H ($CDCl_3$) 7.1–8.1 (8 H, m, arom.), 8.94 (1 H, d, *J* 8.1 Hz, 3-H), 9.96 (1 H, s, CHO), 12.0 (1 H, brs, CONH). δ_C ($CDCl_3$) 119.27, 122.44, 135.63 and 135.65 (4 CH), 121.43 (C2), 140.57 (C1), 126.96 and 128.35 (2 CH of benzoyl, *ortho* and *meta*), 131.65 (CH of benzoyl, *para*), 133.72 (*ipso*-C of benzoyl), 165.24 (CON), 195.29 (CHO).

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Preparation of Dialkyl 1,2-*Dihydroquinoline*-2,3-*dicarboxylates* **5**.—The typical process, exemplified for the preparation of **5a**, is described below.

Preparation of **5a**. To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and 2′-formylacetanilide **2a** (0.161 g, 1 mmol) in CH_2Cl_2 (3 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.142 g, 1 mmol) in CH_2Cl_2 (2 ml) at −10 °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 residue was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using diethyl ether–hexane (1:1) as eluent. The solvent was removed under reduced pressure to afford the product (0.26 g, mp 137–138 °C, 90%) which was recrystallized from ethanol (95%) to yield *dimethyl* N-*acetyl*-1,2-*dihydroquinoline*-2,3-*dicarboxylate* (**5a**) as white crystals (0.24 g), mp 138–139 °C; ν_{max}/cm^{-1} (KBr) 1740 and 1714 (2 C=O, ester), 1668 (C=O, amide); δ_H ($CDCl_3$) 2.32 (3 H, s, CH_3CON), 3.61 and 3.88 (6 H, 2 s, 2 OCH_3), 6.62 (1 H, s, NCH), 7.1–7.5 (4 H, m, arom.), 7.61 (1 H, s, 4-H); δ_C ($CDCl_3$) 22.23 (*C*H_3CON), 51.78 (NCH), 52.29 and 52.69 (2 OCH_3), 124.36, 125.87, 129.00, 130.35 and 134.09 (5 CH), 126.03, 127.21 and 136.41 (3 C), 164.88, 169.24 and 169.68 (3 C=O); *m*/*z* 290 (3%, MH^+, 230 (12%, $MH^+ - CO_2 - CH_4$), 188 (100% $MH^+ - CO_2CH_3 - CH_3CO$), 128 (27%, $MH^+ - 2CO_2CH_3 - CH_3CHO$) [Found: C, 63.8; H, 6.1; N, 4.1%. Calc. for $C_{15}H_{15}NO_5$ (289.29): C, 62.28; H, 5.23; N, 4.84%].

Selected data for **5b**. White crystals (0.28 g), mp 113–114 °C, yielded 87%; ν_{max}/cm^{-1} (KBr) 1735 and 1709 (2 CO=O, ester), 1665 (C=O, amide); δ_H ($CDCl_3$) 1.12 (3 H, t, *J* 7.0 Hz, CH_3 of ester), 1.37 (3 H, t, *J* 7.5 Hz, CH_3 of ester), 2.33 (3 H, s, CH_3CON), 3.80–4.31 (2 H, 2 dq, *J* 7.0 and −10.7 Hz, OCH_2 of ester), 4.35 (2 H, q, *J* 7.5 Hz, OCH_2 of ester), 6.60 (1 H, s, NCH), 7.1–7.5 (4 H, m, arom.), 7.59 (1 H, sm, 4-H); δ_C ($CDCl_3$) 13.97 and 14.29 (2 CH_3 of 2 Et), 22.36 (CH_3 of CH_3CON), 52.12 (NCH), 61.24 and 61.65 (2 OCH_2), 124.40, 125.75, 128.88, 130.14 and 133.65 (5 CH); 126.15, 127.94 and 136.54 (3 C); 164.51, 168.71 and 169.64 (3 C=O); *m*/*z* 318 (2%, MH^+), 244 (17%, $MH^+ - CO_2Et$), 202 (100%, $MH^+ - CO_2Et - CH_3CO$), 174 (45%, $MH^+ - CH_3CO - CO_2Et - CH_2=CH_2$), 128 (25%, $MH^+ - 2CO_2Et - CH_3CHO$) [Found: C, 63.8; H, 6.1; N, 4.1%. Calc. for $C_{17}H_{19}NO_5$ (317.34): C, 64.34; H, 6.04; N, 4.41%].

Selected data for **5c**. Viscous colourless oil (0.35 g), yield 94%; ν_{max}/cm^{-1} (CCl_4) 1732 and 1702 (2 C=O, ester), 1670 (C=O, amide); δ_H ($CDCl_3$) 1.29 and 1.57 (18 H, 2 s, 2 Bu^t), 2.32 (3 H, s, CH_3CON), 6.38 (1 H, s, NCH), 7.1–7.4 (4 H, m, arom.), 7.45 (1 H, s, 4-H); δ_C ($CDCl_3$) 27.81 and 28.18 (6 CH_3, 2 Bu^t), 52.73 (NCH), 81.48 and 82.30 (2 C, 2 Bu^t), 124.36, 125.46, 128.60, 129.82 and 132.30 (5 CH), 126.32, 128.60 and 136.62 (3 C), 163.78, 167.81 and 169.56 (3 C=O); *m*/*z* 374 (2%, MH^+), 272 (4%, $MH^+ - CO_2 - Me_3CH$), 230 (7%, $MH^+ - CO_2Bu^t - CH_3CO$), 174 (100%, $MH^+ - CO_2Bu^t - CH_3CO$, $CH_2=CMe_2$) [Found: C, 68.3; H, 7.3; N, 4.2%. Calc. for $C_{21}H_{27}NO_5$ (373.45): C, 67.54; H, 7.29; N, 3.75%].

Selected data for **5d**. White crystals (0.29 g), mp 160–161 °C, yield 83%; ν_{max}/cm^{-1} (KBr) 1740 and 1705 (2 C=O, ester), 1645 (C=O, amide); δ_H ($CDCl_3$) 3.63 and 3.89 (6 H, 2 s, 2 OCH_3), 6.46 (1 H, s, NCH), 6.7–7.6 (9 H, m, arom.), 7.69 (1 H, s, 4-H); δ_C ($CDCl_3$) 52.59 and 52.73 (2 OCH_3), 53.50 (NCH), 125.01, 125.14, 129.78, 131.04 and 134.22 (5 CH of quinoline), 128.27 and 129.04 (2 CH of benzoyl, *ortho* and *meta*), 128.80 (CH of benzoyl, *para*), 134.30 (*ipso*-C of benzoyl), 126.37, 129.05 and 137.35 (3 C of quinoline), 164.84, 169.11 and 169.44 (3 C=O); *m*/*z* 352 (4%, MH^+), 294 (10%, $MH^+ - CO_2 - CH_4$), 156 (15%, $MH^+ - CO_2CH_3 - OCH_3$, C_6H_5CHO), 128 (20%, $MH^+ - 2\ CO_2CH_3 - C_6H_5CHO$) 105 (100%, $C_6H_5CO^+$) [Found: C, 67.7; H, 4.9; N, 3.6%. Calc. for $C_{20}H_{17}NO_5$ (351.36): C, 68.37; H, 4.88; N, 3.99%].

Selected data for **5e**. White crystals (0.33 g), mp 76-5–78 °C, yield 88%; ν_{max}/cm^{-1} (KBr) 1730 and 1691 (2 C=O, ester), 1665 (C=O, amide); δ_H ($CDCl_3$) 1.14 (3 H, t, *J* 7.2 Hz, CH_3 of ester), 1.37 (3 H, t, *J* 7.0 Hz, CH_3 of ester), 3.80–4.31 (2 H, 2 dq, *J* 7.2 and −10.8 Hz, OCH_2 of ester), 4.35 (2 H, q, *J* 7.0 Hz, OCH_2 of ester), 6.43 (1 H, s, NCH), 6.7–7.6 (9 H, m, arom.), 7.66 (1 H, s, 4-H); δ_C ($CDCl_3$) 13.93 and 14.29 (2 CH_2CH_3), 53.51 (NCH), 61.24 and 61.69 (2 OCH_2), 125.12, 125.13, 129.66, 131.00 and 134.42 (5 CH of quinoline), 128.31 and 129.04 (2 CH of benzoyl, *ortho* and *meta*), 128.72 (CH of benzoyl, *para*), 133.77 (*ipso*-C of benzoyl), 127.01, 129.05 and 137.39 (3 C of quinoline), 164.47, 168.62 and 169.56 (3 C=O); *m*/*z* 380 (3%, MH^+), 306 (100%, $MH^+ - 2\ CH_2=CH_2 - H_2O$), 279 (15%, $MH^+ - CO_2Et - CH_2=CH_2$), 105 ($C_6H_5CO^+$) [Found: C, 69.0; H, 5.7; N, 3.4%. Calc. for $C_{22}H_{21}NO_5$ (379.42): C, 69.65; H, 5.58; N, 3.69%].

Selected data for **5f**. White crystals (0.41 g), mp 128.5–130 °C, yield 95%; ν_{max} cm^{-1} KBr 1735 and 1699 (2 C=O, ester), 1647 (C=O, amide); δ_H ($CDCl_3$) 1.32 and 1.56 (18 H, 2 s, 2 Bu^t), 6.24 (1 H, s, NCH), 6.7–7.5 (9 H, m, arom.), 7.53 (1 H, s, 4-H). δ_C ($CDCl_3$) 27.81 and 28.06 (6 CH_3, Bu^t), 54.28 (NCH), 81.36 and 82.28 (2 C, 2 Bu^t), 124.85, 125.05, 129.29, 130.80 and 132.38 (5 CH of quinoline), 128.23 and 128.84 (2 CH of benzoyl, *ortho* and *meta*), 128.39 (CH of benzoyl, *para*), 134.70 (*ipso*-C of benzoyl), 125.30, 128.85 and 137.35 (3 C of quinoline), 163.62, 167.65 and 169.48 (3 C=O); *m*/*z* 436 (2%, MH^+), 334 (100%, $MH^+ - CO_2 - Me_3CH$), 306 (15%, $MH^+ - 2\ CH_2=CMe_2 - H_2O$), 278 (50%, $MH^+ - CO_2 - Me_3CH - CH_2=CMe_2$), 156 (10%, $MH^+ - CO_2Bu^t - OBu^t - C_6H_5CHO$), 105 (25%, $C_6H_5CO^+$), 174 (100%, $MH^+ - CO_2Bu^t - CH_3CO$, $CH_2=CMe_2$ [Found: C, 71.3; H, 6.8; N, 3.4%. Calc. for $C_{26}H_{29}NO_5$ (435.52): C, 71.70; H, 6.71; N, 3.22%].

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