Vinyltriphenylphosphonium Salt Mediated Serendipitous Synthesis of a Functionalized Pyrroloisoindole Derivative. New Synthesis of Trimethyl 5-Arylpyrrole-2,3,4-tricarboxylates†

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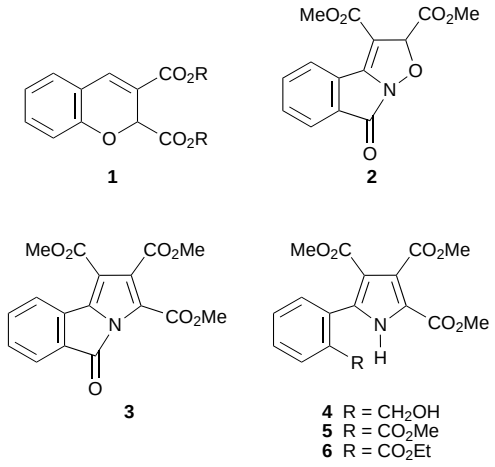
Issa Yavari* and Mohammad Reza Islami

Chemistry Department, Tarbiat Modarres University, P.O. Box 14155-4838, Tehran, Iran

N-Hydroxyphthalimide undergoes a complex reaction with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine yielding a multiply functionalized pyrroloisoindole derivative which is then converted to trimethyl 5-arylpyrrole-2,3,4-tricarboxylate derivatives.

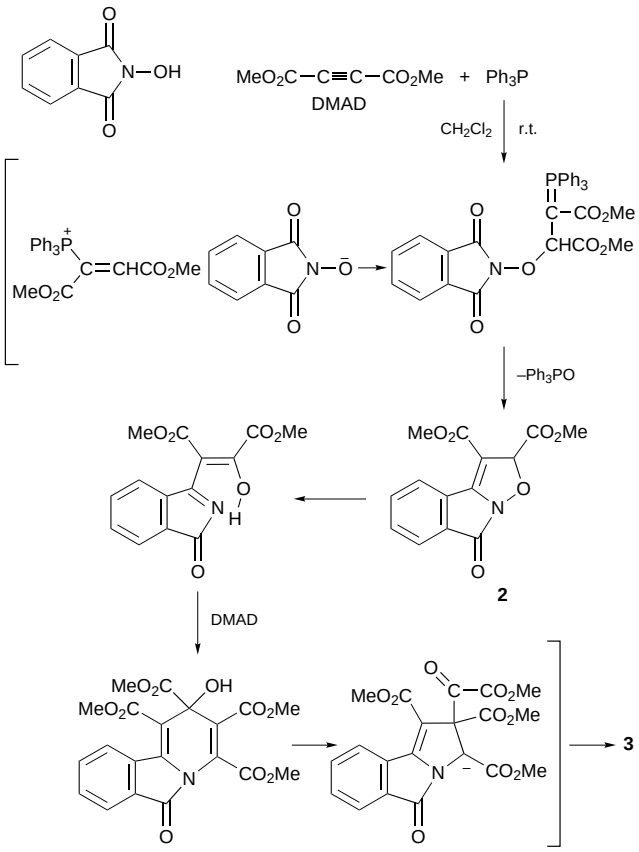
We have recently described[1] the synthesis of functionalized 2*H*-chromene derivatives **1** from the reaction of triphenylphosphine, 2-hydroxybenzaldehyde and dialkyl acetylenedicarboxylates using an intramolecular Wittig reaction.[2–6] With the purpose to prepare isoindoloisoxazoles, *e.g.* **2**, *N*-hydroxyphthalimide was treated with dimethyl acetylenedicarboxylate (DMAD) and triphenylphosphine. However, the isoindoloisoxazole derivative **2** was not observed but trimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]isoindole-2,3,4-tricarboxylate (**3**) was isolated in fairly high yield. Compound **3** was converted to the densely functionalized pyrrole derivatives **4**–**6**.



The structures of compounds **3–6** were deduced from their elemental analyses and their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at *m*/*z* 343, 347, 375 and 389, respectively. The base peak in the mass spectra of compounds **3** and **4** corresponds to $M^+ - OCH_3$. Any initial fragmentation involved the loss of ester moieties.

The ^{1}H and ^{13}C NMR data for compounds **3–6** are shown in Table 1. The ^{1}H NMR spectrum of **3** exhibited three single sharp lines readily recognizable as arising from methoxy (δ 3.91, 3.92 and 3.94) protons along with a fairly complex multiplet in the aromatic region. The noise-decoupled ^{13}C NMR spectrum of **3** showed 17 distinct resonances in agreement with the pyrroloisoindole structure. Partial assignments of these resonances are given in Table 1.

Several examples are known in which a heterocyclic alkene is formed from a phosphorane connected to a carbonyl group by a chain containing a heteroatom.[1–6] Thus the isoindoloisoxazole derivative **2** (see Scheme 1) may be considered as the primary product of an intramolecular Wittig reaction. Such an addition–cyclization product apparently results from the initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct, followed by attack of the anion of *N*-hydroxyphthalimide on the vinyltriphenylphosphonium cation to form the phosphorane, which is converted into **2**.



Scheme 1

We have not established a mechanism for the formation of trimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]isoindole-2,3,4-tricarboxylate (**3**), but a reasonable possibility is indicated in Scheme 1. The final step of this mechanism involves the loss of a MeO_2C-CO group as a negatively charged entity. Although this step may seem uncommon, migration of alkoxycarbonyl groups as negatively charged species are not unknown.[7]

Compound **3** can be reduced to trimethyl 5-(2-hydroxymethylphenyl)pyrrole-2,3,4-tricarboxylate (**4**) using sodium borohydride in dimethylformamide–methanol (1:1). The ^{1}H

*To receive any correspondence.

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Table 1 Proton and ^{13}C NMR data for compounds **3–6**

Compound	$^1H/^{13}C$	δ (ppm) ($CDCl_3$–Me_4Si)
3	^1H	3.91, 3.92 and 3.94 (9 H, 3 s, 3, OCH_3), 7.2–8.2 (4 H, m, Ar)
	^{13}C	52.28, 52.61 and 52.81 (9 H, 3 s, 3 OCH_3), 111.21, 121.27, 130.52, 130.75, 132.79 and 142.16 (6 C), 124.85, 126.44, 130.43 and 135.64 (4 CH), 158.16, 160.65, 161.95 and 163.98 (4 C=O)
4	^1H	3.0 (1 H, br s, OH), 3.68, 3.82 and 3.94 (9 H, 3 s, 3 OCH_3), 4.50 (2 H, s, CH_2), 7.3–7.6 (4 H, m, Ar), 10.8 (1 H, br s, NH)
	^{13}C	51.63, 52.28 and 52.77 (3 OCH_3), 63.4 (CH_2), 112.96, 119.73, 124.32, 129.83, 129.90 and 138.90 (6 C), 127.62, 129.74, 131.57 and 138.70 (4 CH), 160.20, 163.62 and 166.26 (3 C=O)
5	^1H	3.58, 3.66, 3.69 and 3.95 (12 H, 4 s, 4 OCH_3), 7.3–8.1 (4 H, m, Ar), 10.3 (1 H, br s, NH)
	^{13}C	50.90, 51.79, 51.81 and 52.20 (4 OCH_3), 112.47, 123.91, 128.88, 129.73, 130.83 and 131.40 (6 C), 118.74, 130.91, 131.08 and 139.18 (4 CH), 160.27, 162.64, 165.61 and 166.38 (4 C=O)
6	^1H	1.11 (3 H, t, J = 7.2 Hz, CH_3), 3.58, 3.68 and 3.94 (9 H, 3 s, 3 OCH_3), 4.12 (2 H, q, J 7.2 Hz, OCH_2), 7.3–8.1 (4 H, m, Ar), 10.3 (1 H, br s, NH)
	^{13}C	13.72 (CH_3), 51.35, 52.29 and 52.69 (3 OCH_3), 61.20 (OCH_3), 112.96, 124.36, 129.29, 130.27, 131.20 and 131.62 (6 C), 118.99, 131.41, 131.60 and 139.84 (4 CH), 160.68, 163.05, 166.10 and 166.55 (4 C=O)

NMR spectrum of **4** displayed four single sharp resonances for methoxy (δ 3.68, 3.82 and 3.94) and methylene (δ 4.50) protons, along with a multiplet in the aromatic region as well as two fairly broad peaks at δ 3.0 and 10.8 for the OH and NH groups, respectively. The latter signals rapidly disappeared on addition of D_2O. The noise-decoupled ^{13}C NMR spectrum of **4** is similar to that of **3**, except for the presence of a new resonance at δ 63.40 for the CH_2-O group, and the absence of one of the carbonyl resonances (see Table 1).

The nitrogen atom of the five-membered lactam incorporated in structure **3** is a pyrrole nitrogen and the pyrrole ring has three electron-withdrawing ester groups. Thus, the peptide linkage is expected to be fairly labile to nucleophilic attack and opening. Although compound **3** is stable in hot ethanol and can be recrystallized from this solvent, it undergoes a smooth reaction with strong nucleophiles, such as alkoxide ions.[8] When compound **3** was treated with sodium methoxide in methanol at room temperature it was converted to the tetracarboxylate **5** in 96% yield. The same reaction, using sodium ethoxide in ethanol, provided trimethyl 5-(2-ethoxycarbonylphenyl)pyrrole-2,3,4-tricarboxylate (**6**) in 90% yield. The ^1H and ^{13}C NMR spectra of compounds **5** and **6** are given in Table 1. The ^{13}C chemical shifts of **5** and **6** are similar to those of **4**, except for the presence of a new alkoxycarbonyl moiety, and the absence of the hydroxymethyl resonance (see Table 1).

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H and N were performed using a Heracus CHN-O-Rapid analyser. IR spectra were measured on a Shimadzu IR-460 spectrometer. UV spectra were measured for solutions in ethanol (95%) on a Shimadzu UV-2100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a 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. *N*-Hydroxyphthalimide and dimethyl acetylenedicarboxylate were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of Trimethyl 9-oxo-9H-pyrrolo[1,2-a]*isoindole-2,3,4-tricarboxylate* (**3**).—To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol) and *N*-hydroxyphthalimide (0.16 g, 1 mmol) in dichloromethane (15 ml), a mixture of dimethyl acetylenedicarboxylate (0.24 ml, 2 mmol) in dichloromethane (2 ml) at −10 °C was added dropwise over 10 min. The reaction mixture was then allowed to warm up to room temperature and then stirred for 24 h. The solvent was removed under reduced pressure and ethanol (20 ml) was added. The product was obtained by filtration and washed with ethanol (10 ml). Recrystallization from ethanol gave yellow crystals of trimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]isoindole-2,3,4-tricarboxylate **3**, 0.32 g, mp 178–180 °C, yield 95%, ν_{max} (KBr) cm^{-1}: 1794 (C=O, lactam), 1742, 1716 and 1714 (C=O, ester). *m/z* 343 (M^+, 55%), 312 ($M^+ - OCH_3$, 100), 195 ($M^+ - 2CO_2CH_3 - OCH_2$, 65), 194 ($M^+ - 2CO_2CH_3 - OCH_3$, 5) (Found: C, 59.1; H, 4.0; N, 4.0. $C_{17}H_{15}HO_7$ requires C, 59.48; H, 3.82; N, 4.08%).

Preparation of Trimethyl 5-(2-Hydroxymethylphenyl)pyrrole-2,3,4-tricarboxylate (**4**).—To a magnetically stirred solution of **3** (0.34 g, 1 mmol) in *N*,*N*-dimethylformamide–methanol (1:1, 6 ml), a mixture of sodium borohydride (0.04 g, 1 mmol) in cold methanol (5 ml) was added dropwise. The reaction mixture were stirred for 10 min and then HCl (2 ml, 2.5 M) and water (20 ml) was added and the resulting mixture extracted with chloroform (3 × 10 ml). The organic phase was dried over Na_2SO_4. Removal of the solvent under reduced pressure gave an oily residue which was purified by silica gel (Merck silica gel 60, 230–400 mesh) column chromatography using diethyl ether–ethyl acetate–heptane (1.5:1:1.5) as eluent. The solvent was removed under reduced pressure and trimethyl 5-(2-hydroxymethylphenyl)pyrrole-2,3,4-tricarboxylate **4** was obtained as light yellow oil, 0.17 g, yield 50%, ν_{max} (KBr) cm^{-1} 3440 (OH), 3255 (NH), 1735, 1718 and 1713 (3C=O). *m/z* 347 (M^+, 40%), 316 ($M^+ - OCH_3$, 100), 284 ($M^+ - 2OCH_3 - H$, 90), 298 ($M^+ - OH_3 - H_2O$, 25). (Found: C, 58.6; H, 5.2; N, 3.5, $C_{17}H_{17}NO_7$ requires C, 58.79; H, 4.93; N, 4.03%).

Preparation of Trimethyl 5-(2-Methoxycarbonylphenyl)pyrrole-2,3,4-tricarboxylate (**5**). *General Procedure*.—To a magnetically stirred solution of **3** (0.34 g, 1 mmol) in methanol (5 ml), a mixture of sodium methoxide (0.11 g, 2 mmol) in methanol (5 ml) was added dropwise. The reaction mixture was stirred for 30 min at room temperature and then water (5 ml) was added. After neutralization with HCl (0.1 M), the mixture was extracted with chloroform (3 × 10 ml). The combined chloroform solution was dried over Na_2SO_4. The product (light yellow oil, 0.36 g, yield 0.96%) was obtained by removal of the solvent under reduced pressure. ν_{max} (KBr)/cm^{-1} 3250 (NH), 1723, 1715, 1696 and 1698 (C=O, ester); *m/z* 375 (M^+, 74%), 343 (M^+ – MeOH, 70), 312 (343 – OCH_3, 100), 284 (343 – CO_2Me, 22) (Found: C, 57.3; H, 4.5; N, 3.7. $C_{18}H_{17}NO_8$ requires C, 57.61; M, 4.57; N, 3.73%).

Selected Data for **6**.—Light yellow oil (0.35 g, yield 90%). ν_{max} (KBr)/cm^{-1} 3240 (NH), 1715, 1710 1696 and 1690 (C=O, ester); *m/z* 389 (M^+, 60%), 343 (M^+ – EtOH, 45), 312 (343 – OCH_3, 100), 222 (312 – OMe – CO_2Me, 42). (Found: C, 56.7; H, 4.9; N, 3.7. $C_{19}H_{19}NO_8$ requires C, 56.62; H, 4.92; N, 3.60%).

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8 We are grateful to a referee of this paper for suggesting reaction of **3** with nucleophiles.