New Synthesis of Tetraalkyl 2,3-Dihydro-5-oxopyrrolo[2,1-*a*]isoindole-1,2,3,3-tetracarboxylates and Tetraalkyl 2,3-Dihydro-5-oxopyrrolo[2,1-*a*]-pyrrolidine-1,2,3,3-tetracarboxylates Mediated by Vinyltriphenylphosphonium Salts†

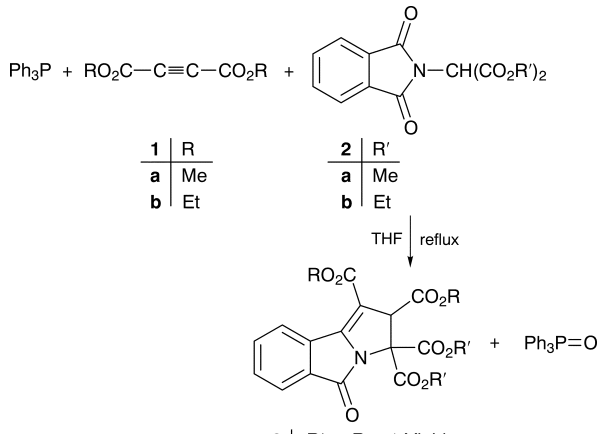
J. Chem. Research (S), 1998, 714–715†

Issa Yavari* and Abbas Ali Esmaili

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

Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by CH-acids, such as dialkyl phthalimidomalonates and dimethyl succinimidomalonate, leads to a vinylphosphonium salt, which undergoes intramolecular Wittig reaction to produce the title compounds in fairly high yields.

Heterocyclic fused-ring systems with ring-junction nitrogen atoms are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[1] Fused pyrrole ring systems, in particular pyrroloisoindole derivatives, are generally the most difficult to prepare using conventional cyclization methods.[1] Current synthetic methodology for preparation of this class of compounds still remains very specific.[2–4] Recently we have established a heterocyclic synthesis using a novel approach to vinyl triphenylphosphonium salts.[5,6] We have extended this reaction to include the use of CH-acids such as dialkyl phthalimidomalonates **2a** and **2b**.[7] Herein we describe a facile one-pot synthesis of the fused heterocyclic ring system **3**. Thus, reaction of phthalimidomalonates **2** with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine leads to **3** in fairly good yields.

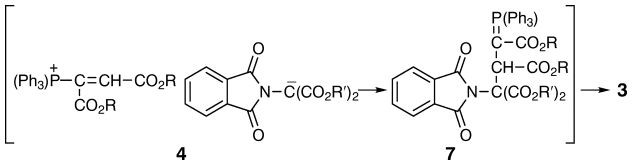


1	R
a	Me
b	Et

2	R′
a	Me
b	Et

3	R′	R	% Yield
a	Me	Me	95
b	Me	Et	90
c	Et	Me	87
d	Et	Et	85

On the basis of the chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that the fused-ring system **3** results from the initial addition of triphenylphosphine to the acetylenic ester and a concomitant protonation of the reactive 1:1 adduct, followed by attack of the conjugate base of the CH-acid on the vinyltriphenylphosphonium cation to produce the phosphorane **5**, which is converted into **3**.



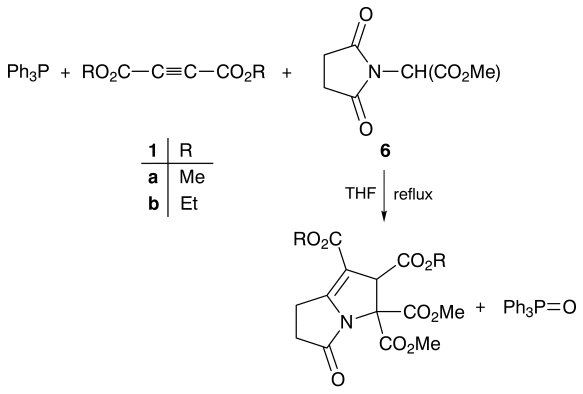
The ^{1}H NMR spectrum of **3a** exhibited four single sharp lines readily recognizable as arising from the methoxy (δ 3.76, 3.84, 3.87 and 3.89) protons, along with a singlet at δ 5.15 from the methine proton. A fairly complex multiplet was observed for the aromatic protons at δ 7.4–8.6 (see Table 1).

The ^{13}C NMR spectrum of **3a** displayed nineteen distinct resonances in agreement with the dihydropyrroloisoindole structure. Partial assignments of these resonances are given in Table 1.

When dimethyl succinimidomalonate **6**[7] was allowed to react with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine in tetrahydrofuran, tetraalkyl 2,3-dihydro-5-oxopyrrolo[2,1-*a*]pyrrolidine-1,2,3,3-tetracarboxylates **7** were obtained in fairly high yields.

The ^{1}H and ^{13}C NMR spectra of **7a** and **7b** are similar to those of **3a** and **3b**, respectively, except for the imide residue, which displayed characteristic resonances with appropriate chemical shifts (see Table 1).

The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches.[2–4] Further investigations of the present method will be required to establish its scope and limitations.



1	R
a	Me
b	Et

7	% Yield
a	95
b	85

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 ^1H and ^3C NMR data for compounds **3** and **7**

Compound	$^1H/^{13}C$	δ (ppm) ($CDCl_3$–Me_4Si)
3a	^1H	3.76, 3.84, 3.87 and 3.89 (12 H, 4 s, 4 OCH_3), 5.15 (1 H, s, CH), 7.4–8.1 (3 H, m, 3 CH, arom.), 8.60 (1 H, dd, *J* 8.5 and 2.5, arom. CH *ortho* to C=O group)
	^{13}C	52.04, 53.02, 54.00 and 54.32 (4 OCH_3), 60.88 (CH), 71.18 (C), 105.10 (^{13}C=C–N), 124.16, 127.37, 132.51 and 133.16 (4 CH, arom.), 129.13 and 135.23 (2 C arom.), 149.89 (C^{13}C–N), 162.11, 163.37, 164.84, 166.71 and 169.07 (5 C=O)
3b	^1H	1.34 and 1.42 (6 H, 2 t, *J* 7.2, 2 CH_3), 3.84 and 3.90 (6 H, 2 s, 2 OCH_3), 4.21 and 4.34 (4 H, 2 q, *J* 7.2, 2 OCH_2), 5.15 91 H, s, CH), 7.5–8.1 (3 H, m, 3 CH arom.), 8.62 (1 H, dd *J* 8.4 and 2.4, arom. CH *ortho* to C=O)
	^{13}C	13.60 and 13.84 (2 CH_3), 53.38 and 53.79 (2 OCH_3), 60.61 (CH), 60.63 and 61.65 (2 OCH_2), 70.73 (C), 105.30 (^{13}C=C–N), 123.92, 131.97 and 132.62 (4 CH, arom.), 128.72 and 134.78 (2 C, arom.), 149.24 (C=^{13}C–N), 161.62, 162.47, 164.31, 166.30 and 168.26 (5 C=O)
3c	^1H	1.31 and 1.32 (6 H, 2 t, *J* 7.2, 2 CH_3), 3.72 and 3.80 (6 H, 2 s, 2 OCH_3), 4.32 and 4.36 (4 H, 2 q, *J* 7.2, 2 OCH_2), 5.18 (1 H, s, CH), 7.5–8.1 (3 H, m, 3 CH arom.), 8.55 (1 H, dd, *J* 8.5 and 2.4, arom. CH *ortho* to C=O)
	^{13}C	13.35 and 13.40 (2 CH_3), 51.47 and 52.28 (2 OCH_3), 60.14 (CH), 62.91 and 63.11 (2 OCH_2), 70.85 (C), 104.57 (^{13}C=C–N), 123.50, 126.80, 131.97 and 132.58 (4 CH arom.), 128.59 and 134.78 (2 C arom.), 149.48 (C=^{13}C–N), 161.50, 162.88, 163.82, 165.69 and 168.50 (5 C=O)
3d	^1H	1.2–1.4 (12 H, m, 4 CH_3), 4.0–4.6 (8 H, m, 4 OCH_2), 5.15 (1 H, s, CH), 7.5–8.1 (3 H, m, 3 CH arom.), 8.60 (1 H, dd, *J* 8.4 and 2.5, arom. CH *ortho* to C=O)
	^{13}C	13.90, 13.93, 14.01 and 14.29 (4 CH_3), 60.84 (CH), 61.00, 61.94, 63.28 and 63.57 (4 OCH_2), 71.38 (C), 105.79 (^{13}C=C–N), 124.08, 127.37, 132.26 and 132.91 (4 CH arom.), 129.29 and 135.44 (2 C arom.), 149.89 (C=^{13}C–N), 162.11, 163.09, 164.31, 166.30 and 168.71 (5 C=O)
7a	^1H	2.90, 3.10 (4 H, ABCD system, 2 CH_2), 3.71, 3.73, 3.79 and 3.88 (12 H, 4 s, 4 OCH_3), 4.90 (1 H, s, CH)
	^{13}C	20.97 and 33.19 (2 CH_2), 51.43, 52.82, 53.91 and 54.28 (4 OCH_3), 59.66 (CH), 71.67 (C), 99.89 (^{13}C=C–N), 161.05 (C=^{13}C–N), 163.98, 164.31, 166.34, 169.44 and 170.45 (5 C=O)
7b	^1H	1.25 and 1.29 (6 H, 2 t, *J* 7.2, 2 CH_3), 2.70, 3.30 (4 H, ABCD system, 2 CH_2), 3.80 and 3.95 (2 OCH_3), 4.16 and 4.18 (4 H, 2 q, *J* 7.2, 2 CH_2), 4.85 (1 H, s, CH)
	^{13}C	13.76 and 14.05 (2 CH_3), 20.60 and 32.98 (2 CH_2), 53.46 and 53.95 (2 OCH_3), 59.57 (CH), 59.90 and 61.65 (2 OCH_2), 71.42 (C), 100.21 (^{13}C=C–N), 160.36 (C=^{13}C–N), 163.29, 163.94, 166.14, 168.83 and 170.13 (5 C=O)

a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 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.

Preparation of Dialkyl Imidomalonates **2a**, **2b** *and* **6**.—Compounds **2a**, **2b** and **6** were prepared from dialkyl bromomalonates and the corresponding imides by known methods[7] and identified as follows. Dimethyl phthalimidomalonate (**2a**): white crystals; mp 110–111 °C; ν_{max}/cm^{-1} (KBr) 1710 and 1745 (C=O); δ_H ($CDCl_3$): 3.95 (6 H, s, 2 OCH_3), 5.58 (1 H, s, NCH), 7.6–8.1 (4 H, AA′BB′ system, arom.); δ_C ($CDCl_3$): 53.02 (2 OCH_3), 53.67 (NCH), 123.42 and 134.25 (4 CH), 131.12 (C arom.), 164.39 and 165.98 (2 C=O). Diethyl phthalimidomalonate (**2b**): white crystals, mp 73–74 °C; ν/cm^{-1} (KBr) 1710 and 1745 (C=O); δ_H ($CDCl_3$) 1.35 (6 H, t, *J* 7.2, 2 CH_3), 4.30 (4 H, q, *J* 7.2, 2 OCH_2), 5.50 (1 H, s, NCH), 7.6–8.1 (4 H, AA′BB′ system, arom.); δ_C ($CDCl_3$): 13.31 (2 CH_3), 53.87 (NCH), 62.06 (2 OCH_2), 123.14 and 134.05 (4 CH arom.), 130.96 (C arom.), 163.78 and 165.77 (2 C=O).

Dimethyl succinimidomalonate (**6**): pale yellow crystals; mp 80–82 °C; ν/cm^{-1} (KBr) 1705 and 1740 (C=O); δ_H ($CDCl_3$) 2.83 (4 H, s, 2 CH_2), 3.80 (6 H, s, 2 OCH_3), 5.35 (1 H, s, NCH); δ_C ($CDCl_3$) 27.57 (2 CH_2), 62.65 (2 OCH_3), 53.75 (NCH), 163.72 and 175.14 (2 C=O).

Preparation of Tetraalkyl 2,3-*Dihydro*-5-*oxopyrrolo*[2,1-*a*]*isoindole*-1,2,3,3-*tetracarboxylate* **3**.—The typical process for the preparation of tetramethyl 2,3-dihydro-5-oxopyrrolo[2,1-*a*]isoindole-1,2,3,3-tetracarboxylate (**3a**) is described as an example. To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol) and dimethyl phthalimidomalonate (0.554 g, 2 mmol) in THF (5 ml) was added dropwise a mixture of dimethyl acetylenedicarboxylate (0.284 g, 2 mmol) in THF (2 ml) at −10 °C over 10 min. The reaction mixture was then allowed to warm to room temperature then refluxed for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to yield **3a** as white *crystals* (0.38 g, 95%), mp 159–160 °C; ν/cm^{-1} (KBr) 1767, 1733, 1697, and 1653 (C=O); *m*/*z* (%): 404 (M^++1, 2), 372 (M^++1 − MeOH, 9), 345 (M^++1 − CO_2Me, 12), 313 (M^++1 − CO_2Me − MeOH, 100), 59 (M^+ of CO_2Me, 55) (Found: C, 56.7; H, 4.3; N, 3.4. $C_{19}H_{17}NO_9$ (403.34) requires C, 56.58; H, 4.25; N, 3.47%).

Selected data for **3b**.—Mp 139–140 °C; yield 0.78 g (90%). ν/cm^{-1} (KBr) 1768, 1742, 1701 and 1659 (C=O); *m*/*z* (%) 433 (M^++1, 40); 400 (M^+ − MeOH, 10), 327 (M^++1 − CO_2Et − MeOH, 100), 254 (M^++1 − 2CO_2Et − MeOH, 77), 59 (M^+ of CO_2Me, 16). (Found: C, 58.6; H, 5.0; N, 3.3. $C_{21}H_{21}NO_9$ (431.40) requires C, 58.47; H, 4.91; N, 3.25%).

Selected data for **3c**.—Mp 120–122 °C; yield 0.75 g (87%). ν/cm^{-1} (KBr) 1763, 1738, 1695 and 1659 (C=O); MS (*m*/*z*, %): 433 (M^++1, 4), 386 (M^++1 − EtOH, 5), 327 (M^++1 − CO_2Et − MeOH, 100), 268 (M^++1 − 2CO_2Me-EtOH, 70), 254.4 (M^++1 − 2CO_2Et − MeOH, 90), 240 (M^++1 − CO_2Et − 2CO_2Me, 70), 196 (M^++1 − 2CO_2Et − CO_2Me, 100); 59 (M^+ of CO_2Me, 80). (Found: C, 58.6; H, 5.0; N, 3.3. $C_{21}H_{21}NO_9$ (431.40) requires C, 58.47; H, 4.91; N, 3.25%).

Selected data for **3d**.—Mp 120–122 °C; yield 0.78 g (85%). ν/cm^{-1} (KBr) 1768, 1731, 1699 and 1665 (C=O); *m*/*z* (%): 461 (M^++1, 5), 387 (M^++1 − CO_2Et, 5), 341 (M^++1 − CO_2Et − EtOH, 54), 268 (M^++1 − 2CO_2Et − 2CO_2Me, 100), 196 (M^++1 − 3CO_2Et − OEt). (Found: C, 60.1; H, 5.5; N, 3.0. $C_{23}H_{25}NO_9$ (459.45) requires C, 60.13; H, 5.49; N, 3.05%).

Selected data for **7a**.—Mp 132–134 °C; yield 0.64 g (90%). ν/cm^{-1} (KBr) 1767, 1750, 1735, 1690 and 1645 (C=O); *m*/*z* (%): 357 (M^++1, 45), 296 (M^++1 − CO_2Me, 79), 266.3 (M^++1 − CO_2Me − MeOH, 87), 121 (M^++1 − 4CO_2Me, 100) (Found: C, 50.8; H, 4.9; N, 4.0. $C_{15}H_{17}NO_9$ (355.30) requires C, 50.71; H, 4.82; N, 3.94%).

Selected data for **7b**.—Mp 91–93 °C; yield 0.64 g (85%). ν/cm^{-1} (KBr) 1767, 1750, 1735, 1690 and 1645 (C=O); *m*/*z* (%): 384 (M^++1, 45), 325 (M^++1 − CO_2Me, 49), 311 (M^++1 − CO_2Et, 59), 293.3 (M^++1 − CO_2Me − MeOH, 87), 120 (M^++1 − 2CO_2Me, −2CO_2Et, 100) (Found: C, 53.3; H, 5.6; N, 3.7. $C_{17}H_{21}NO_9$ (383.35) requires C, 53.26; H, 5.52; N, 3.65%).

Received, 20th May 1998; Accepted, 28th July 1998
Paper E/8/03804J

References

1 A. R. Katritzky, *Handbook of Heterocyclic Chemistry*. Pergamon Press, Oxford, 1995, 495–505.
2 A. G. Griesbeck, A. Henz, W. Kramer, J. Lex, F. Nerowski, M. Oelgemdler, K. Peters and E. M. Peters, *Helv. Chim. Acta*, 1997, **80**, 912.
3 R. Grigg, M. J. Dorrity and J. F. Malone, *Tetrahedron Lett.*, 1990, **31**, 1343.
4 J. M. Muchowski and P. H. Nelson, *Tetrahedron Lett.*, 1980, **21**, 4585.
5 I. Yavari, A. Ramazani and A. Yahya-Zadeh, *Synth. Commun.*, 1996, **26**, 4495.
6 I. Yavari and R. Baharfar, *J. Chem. Res. (S)*, 1997, 146.
7 A. E. Osterberg, *Org. Synth.*, 1941, **Coll. Vol. I**, 271.
8 D. E. C. Cobridge, *Phosphorus, An Outline of Chemistry, Biochemistry and Uses*, Elsevier, Amsterdam, 1995, 5th edn.