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# Vinylphosphonium Salt Mediated Efficient Synthesis of Dialkyl 1*H*-Pyrrolizine-2,3-dicarboxylates†

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Protonation of the 1:1 intermediate produced in the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates by pyrrole-2-carbaldehyde leads to a vinylphosphonium salt, which undergoes intramolecular Wittig reaction to produce the title compounds in good yields.

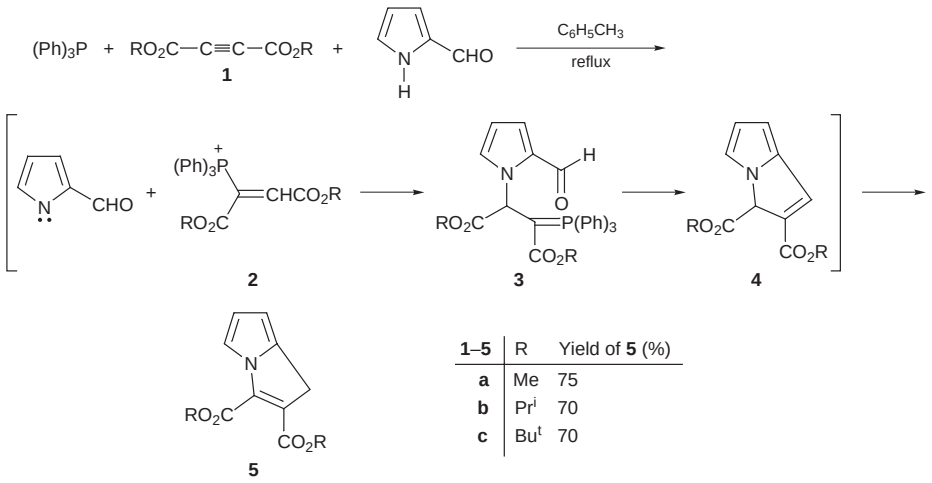
Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[1] The interest in fused pyrrole ring systems, in particular pyrrolizine derivatives, stems from the appearance of saturated and partially saturated pyrrolizine rings in many alkaloids.[2] Herein we describe a facile synthesis of dialkyl 1*H*-pyrrolizine-2,3-dicarboxylates **5**. Thus, reaction of pyrrole-2-carbaldehyde with dialkyl acetylenedicarboxylates **1** in the presence of triphenylphosphine leads to **5** in fairly good yields (see Scheme 1).

Structure **5** was assigned to the isolated products on the basis of their elemental analyses and IR, $^1$H, $^{13}$C NMR and mass spectral data. NMR spectroscopy was used to distinguish structure **5** from the primary product, the 3H pyrrolizine derivative **4**. Thus, the $^1$H NMR spectrum of each of the isolated products exhibited a methylene proton signal at about $\delta$ 4.7. Further evidence was obtained from the $^{13}$C NMR spectra which displayed a methylene carbon resonance at about $\delta$ 55. The mass spectra of 1*H*-pyrrolizine derivatives **5a–c** are similar, as expected, and confirm their molecular weights. Initial fragmentations involve loss of the ester side chains and scission of the rings. The $^1$H NMR spectrum of **5a** exhibited three single sharp lines, readily recognizable as arising from methoxy ($\delta$ 3.88 and 3.92) and methylene ($\delta$ 4.7) protons, along with characteristic resonances for the pyrrole ring system ($\delta$ 6.4–6.8). The $^{13}$C NMR spectrum of **5a** displayed eleven distinct resonances in agreement with the 1*H*-pyrrolizine structure. Partial assignments of these resonances are given in the Experimental section.

The $^1$H and $^{13}$C NMR spectra of **5b** and **5c** are similar to those of **5a**, except for the ester groups, which display characteristic resonances with appropriate chemical shifts (see Experimental section).

Several examples are known in which a heterocyclic alkene is produced from a phosphorane connected to a carbonyl group by a chain containing a heteroatom.[3] Thus, pyrrolizine derivative **5** may be regarded as a product of an intramolecular Wittig reaction. Such addition-cyclization products apparently result from initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1 : 1 adduct, followed by attack of the anion of the NH acid to vinyltriphenylphosphonum cation to form the phosphorane **3**, which is converted into the 3*H*-pyrrolizine derivative **4**. Compound **4** apparently isomerizes, under the reaction conditions, to produce the 1*H*-pyrrolizine isomer **5** (see Scheme 1).

In summary, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches.[4]




| 1–5 | R | Yield of **5** (%) |
|---|---|---|
| **a** | Me | 75 |
| **b** | Pr$^i$ | 70 |
| **c** | Bu$^t$ | 70 |

**Scheme 1**

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

## Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were

measured on a Shimadzu IR-460 spectrometer, $^1$H and $^{13}$C NMR spectra with a Bruker DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively and Mass spectra on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine, dialkyl acetylenedicarboxylates **1** and pyrrole-2-carbaldehyde were obtained from Fluka (Buchs, Switzerland) and used without further purification.

The process for the preparation of dimethyl 1*H*-pyrrolizine-2,3-dicarboxylate **5a** is described as an example. To a magnetically stirred solution of pyrrole-2-carbaldehyde (0.20 g, 2 mmol) and triphenylphosphine (0.52 g, 2 mmol) in toluene (10 ml) was added, dropwise, a mixture of dimethyl acetylenedicarboxylate (0.24 ml, 2 mmol) in toluene (4 ml) at room temperature over 10 min. The reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure and the solid residue purified by silica gel (Merck 230–400 mesh) column chromatography using hexane–ethyl acetate (2 : 1) as eluent. The solvent was removed under reduced pressure and the product **5a** (0.33g, mp. 79–80 °C, yield 75%) obtained as yellow powder. IR (KBr) ($\nu_{max}$/cm$^{-1}$) 1734 and 1730 (C=O). $^1$H NMR: $\delta$ 3.85 and 3.87 (6 H, 2 s, 2 $OCH_3$); 4.76 (2 H, s, $CH_2$); 6.4–6.8 (3 H, m, 3 CH). $^{13}$C NMR: $\delta$ 51.39 and 51.42 (2 $OCH_3$); 55.13 ($CH_2$); 101.88 (CH); 120.12 (C); 121.83 (CH); 123.71 (C); 132.38 (CH); 143.33 (C); 160.44 and 164.47 (2 C=O). MS (*m/z*, %): 221 ($M^+$, 38); 189 (100); 175 (6); 160 (10); 130 (18). (Found: C, 59.8; H, 4.9; N, 6.3. $C_{11}H_{11}NO_4$ requires C, 59.75; H, 5.01; N, 6.33%).

**5b**: viscous yellow oil; 0.85 g, yield 70%. IR (KBr) ($\nu_{max}$/cm$^{-1}$: 1719 and 1716 (C=O); 1685 (C=C). $^1$H NMR: $\delta$ 1.36 and 1.38 (12 H, 2 d, *J* 7.2 4 $CH_3$); 4.70 (2 H, s, $CH_2$); 5.20 and 5.25 (2 H, 2 sept, *J* 7.2 Hz, 2 CH); 6.3–6.7 (3 H, m, 3 CH). $^{13}$C NMR: $\delta$ 21.34 and 21.42 (2 $CHMe_2$); 54.77 ($CH_2$); 67.18 and 67.51 (2 $CHMe_2$); 101.03 (CH); 120.04 (C); 121.55 (CH); 124.56 (C); 131.89 (CH); 142.72 (C); 158.97 and 163.49 (2 C=O). MS (*m/z*, %): 275 ($M^+$, 22) (Found: C, 65.2; H, 6.3; N, 5.2 $C_{15}H_{19}NO_4$ requires C, 65.45; H, 6.22; N, 5.08%).

**5c**: viscous yellow oil, 0.85 g, yield 70%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1710 (C=O); 1685 (C=C). $^1$H NMR: $\delta$ 1.58 and 1.62 (18 H, 2 s, 2 $CMe_3$); 4.69 (2 H, s, $CH_2$); 6.3–6.6 (3 H, m, 3 CH). $^{13}$C NMR: $\delta$ 28.24 and 28.39 (2 $CMe_3$); 55.13 ($CH_2$); 80.40 and 81.33 (2 $CMe_3$); 101.41 (CH); 121.69 (C); 122.37 (CH); 126.19 (C); 131.90 (CH); 142.67 (C); 159.38 and 163.80 (2 C=O. MS (*m/z*, %): 305 ($M^+$, 18) (Found: C, 66.6; H, 7.8; N, 4.9 $C_{17}H_{23}NO_4$ requires C, 66.87; H, 7.58; N, 4.58%).

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