SHORT PAPER

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Synthesis of dialkyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylates mediated by vinylphosphonium salts†

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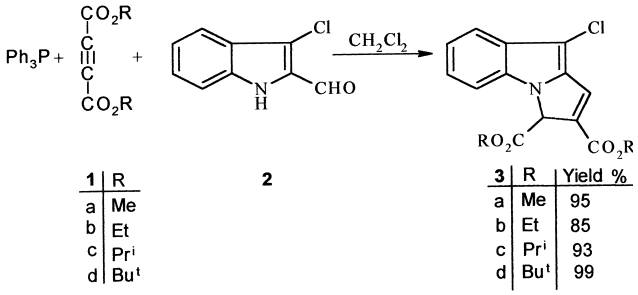
The addition of a dialkyl acetylenedicarboxylate to 3-chloroindole-2-carboxaldehyde in the presence of triphenylphosphine leads initially to a vinylphosphonium salt, which undergoes an intramolecular Wittig reaction to produce the title compounds in fairly good yields.

Keywords: acetylenic esters, triphenylphosphine, 3-chloroindole-2-carboxaldehyde, fused pyrrolizines, indoles, pyrroles

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 biologcal activity.[1] In addition, compounds such as 3*H*-pyrrolo[1,2-*a*]indole are of interest because of the antibacterial activity of related compounds.[2]

While a number of synthetic methodologies for the pyrroloindole ring system have been developed, the literature describing a novel one-pot cyclization method based on consecutive processor is rather scarce.[3]

Herein we describe a facile synthesis of dialkyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylates (**3**). Reaction of 3-chloroindole-2-carboxaldehyde (**2**) with dialkyl acetylenedicarboxylate (**1**) in the presence of triphenylphosphine leads to **3** in fairly high yields (see Scheme 1).



1	R
a	Me
b	Et
c	Pr^i
d	Bu^t

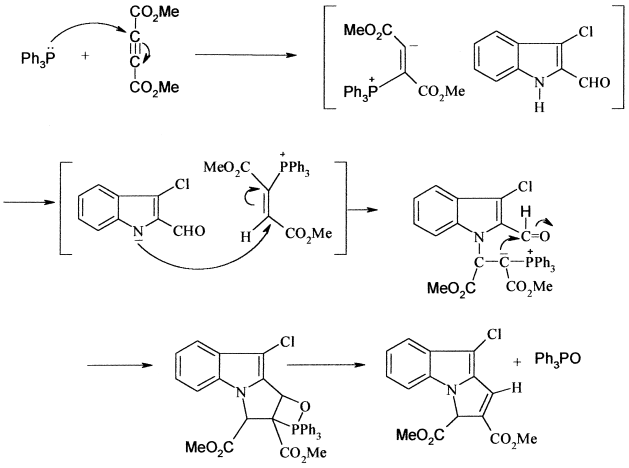
2

3	R	Yield %
a	Me	95
b	Et	85
c	Pr^i	93
d	Bu^t	99

Scheme 1

The pyrroloindole derivatives **3** may be regarded as the product of an intramolecular Wittig reaction. Such addition–cyclisation products apparently result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct, followed by attack of the anion of the 3-chloroindole-2-carboxaldehyde to the vinyltriphenylphosphonium cation to form the phosphorane which is then converted into the 3*H*-pyrrolo[1,2-*a*]indole derivative **3** by intramolecular Wittig reaction with the formyl group. (Scheme 2)

The structures of compounds **3a–d** were deduced from their elemental analyses, ^{1}H and ^{13}C NMR and mass spectral data. In the mass spectra initial fragmentation involves loss the ester side chains. The IR spectra showed bands of medium-strong intensity at *ca* 1740 cm^{-1}, and strong intensity at *ca*



Scheme 2

1715 cm^{-1}, from the unconjugated and conjugated ester carbonyls, respectively.

The ^{1}H NMR spectrum of **3a** displayed two singlets readily recognisable as arising from methoxy (δ 3.80 and 3.89) protons, and two doublets arising from NCH (δ 5.50), CH_{vin} (δ 7.34), along with a fairly complex multiplet in the aromatic region (see Experimental section). All of the isopropyl methyl groups in **3c** show as separate doublets, because of the presence of the chiral centre at C-3.

The noise-decoupled ^{13}C-NMR spectrum of **3a** showed 15 distinct resonances in agreement with the proposed 3*H*-pyrroloindole structure. Partial assignments of these resonances are given in the Experimental section.

The ^{1}H and ^{13}C NMR spectra of **3b–d** are similar to those of **3a**, except for the signals from the ester groups. The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **3a–d** were supported by measurement of their IR spectra.

In conclusion, vinyltriphenylphosphonium salts have been shown to be useful precursors for a new and efficient synthetic route to 3*H*-pyrroloindole derivatives[4]. The one-pot nature of the present procedure makes it an alternative to multistep approaches[5,6] Further application 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. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Perkin-Elmer

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781 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively, on $CDCl_3$ solutions. Mass spectra were recorded on a Shimadzu GC-MASS-QP1100EX spectrometer operating at an ionisation potential of 70 ev. IR spectra were of solid-phase materials (KBr discs).

Triphenylphosphine and dialkyl acetylenedicarboxylates **1** were obtained from Fluka (Buchs, Switzerland) and were used without further purification. 3-Chloro-1*H*-indole-2-carboxaldehyde (**2**) was prepared by known method.[7]

General procedure for synthesis of dialkyl 9-chloro-3H-pyrrolo[1,2-a]indole-2,3–dicarboxylate (**3**):[5,8] To a magnetically stirred solution of 3-chloro-1*H*-indole-2-carboxaldehyde (1mmol) and triphenylphosphine (1mmol) in dichloromethane (5 ml) was added, dropwise, dialkyl acetylenedicarboxylate (1mmol) in dichloromethane (2 ml) at –10 ºC over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 10 min. The solvent was removed under reduced pressure to afford the product which was recrystallised from ethanol to yield the dialkyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (**3**).

Dimethyl ester **3a**: Yield 0.29 g (95%), m.p. 161.3°C. IR (ν_{max}, cm^{-1}): 1715, 1750 (CO, ester); MS, (*m*/*z*, %): 307 (14.8) / 305 (46.5) (M^+), 248 (28.7) / 246 (89.7) ($M^+ - CO_2Me$), 189 (3.9) / 187 (12.1) (M^+–$2CO_2Me$), 152 (M^+-$2CO_2Me$–Cl, 10.3); Anal: calc. for $C_{15}H_{12}ClNO_4$ (305.71): C, 58.93; H, 3.96; N, 4.58. Found: C, 58.68; H, 3.77; N, 4.56%.

^{1}H NMR: δ = 3.80 and 3.89 (6H, 2s, $2CH_3$), 5.50 (H, br s, NCH), 7.34 (1H, br s, CH_{vinyl}), 7.19–7.64 (4H, m, 4CH); ^{13}C-NMR: δ = 53.73 and 54.78 ($2OCH_3$), 65.20 (CHN), 103.040(C_2), 111.51(C_7), 121.56(C_5), 122.45(C_1), 126.55(C_6), 131.25(C_{8a}), 132.34(C_8), 135.39(C_{4a}), 136.05(C_{9a}), 140.81(C_9), 164.06 and 168.61 (2C = O).

Diethyl ester **3b**: Yield 0.28 g (85%) m.p. 81.8°C. IR (ν_{max}, cm^{-1}): 1720, 1735 (CO, ester); (MS, *m*/*z*, %): 335 (M^+ + 2, 14.0), 333 (M^+, 43.7), 262 ($M^+ + 2 - CO_2Et$, 28.0), 260 ($M^+ - CO_2Et$, 87.5), 234 ($M^+ + 2 - CO_2Et - C_2H_4$, 12.4), 232 ($M^+ - CO_2Et - C_2H_4$, 38.8), 188 ($M^+ + 1 - 2CO_2Et$, 14.5); Anal: calc. for $C_{17}H_{16}ClNO_4$ (333.77): C, 61.18; H, 4.83; N, 4.20. Found: C, 60.46; H, 4.51; N, 4.05%.^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.34 (6H, 2t, 2 CH_3), 4.25–4.43 (4H, m, 2 CH_2), 5.61 (1H, d, *J* = 1.53 Hz, NCH), 7.72 (1H, d, *J* = 1.53 Hz, CH_{vinyl}), 7.71–7.42 (4H, m, $4CH_{arom}$). ^{13}C NMR (25.77 MHz, $CDCl_3$): δ = 14.47 and 14.65 (2 CH_3), 61.57 and 62.83 (2 OCH_2), 64.30 (CHN), 101.4 (C_2), 110.45 (C_7), 120.27 (C_5), 121.22 (C_1), 125.19 (C_6), 130.06 (C_{8a}), 130.71 (C_8), 134.16 (C_{4a}), 135.59 (C_{9a}), 139.80 (C_9), 162.44 and 166.96 (2CO).

Diisopropyl ester **3c**: Yield 0.340 g. (85%), m.p. 90.5°C. IR (KBr) (ν_{max}, cm^{-1}): 1715, 1740 (2 CO, ester); MS, (*m*/*z*, %): 363 (M^+ + 2, 7.6), 361 (M^+, 23.7), 274 ($M^+ + 2 - CO_2Pr^i$, 16.81, 274 (M^+-CO_2Pr^i, 52.5), 234 ($M^+ + 2 - CO_2Pr^i - C_3H_6$, 26.1), 232 ($M^+ - CO_2Pr^i - C_3H_6$, 81.6), 187 ($M^+ + 1 - 2CO_2Pr^i$, 16.9), 43 ($C_3H_7$, 88.1). Anal: calc. for $C_{19}H_{20}ClNO_4$ (361.83): C, 63.07; H, 5.57; N, 3.87. Found: C, 62.07; H, 5.22; N, 3.82 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25, 1.31, 1.36, 1.37 (4 × 3H, 4d, 4 CH_3), 5.11, 5.21 (2 × 1H, 4h, 2 CH), 5.55 (1H, d, *J* = 1.68 Hz, NCH),7.65 (1H,1d, *J* = 1.68 Hz, CH_{vinyl}), 7.2–7.7 (4H, m, 4 CH_{arom}); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 23.12, 23.15, 23.36 and 23.40 (4 CH_3), 65.79 and 70.41 (2 OCH), 71.99 (CHN), 102.44 (C_2), 111.56 (C_7), 121.44 (C_5), 122.27 (C_1), 126.18 (C_6), 131.26 (C_{8a}), 131.83 (C_8), 135.35 (C_{4a}), 137.28 (C_{9a}), 141.08 (C_9), 163.20 and 167.65 (2CO).

Di-t-butyl ester **3d**: Yield 0.381 g (99%), m.p. 102.8°C. IR(KBr) (ν_{max}, cm^{-1}): 1710, 1740 (CO ester); MS, (*m*/*z*, %): 391 (M^+ + 2, 3.9), 389 (M^+, 12.2), 290 ($M^+ + 2 - CO_2Bu^t$, 3.3), 288 ($M^+ - CO_2Bu^t$, 10.2), 234 ($M^+ + 2 - CO_2Bu^t - C_4H_8$, 14.4), 232 ($M^+ - CO_2Bu^t - C_4H_8$, 44.9), 187 ($M^+ + 1 - 2CO_2Bu^t$, 25.6), 57 ($Bu^t$, 88.0). Anal: calc. for $C_{21}H_{24}ClNO_4$ (389.88): C, 64.76; H, 6.22; N, 3.60%. Found: C, 63.75; H, 6.02; N, 3.55%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.50, 1.64 (2 × 9H, 2s, $2Bu^t$), 5.47 (1H, d, *J* = 1.72 Hz, NCH), 7.61 (1H, d, *J* = 1.72 Hz, CH_{vinyl}), 7.2–7.7 (4H, m, $4CH_{arom}$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 26.07 and 26.40 ($6CH_3$, $2Bu^t$), 63.59 and 80.20 (2 $OCMe_3$), 81.59 (NCH), 98.55 (C_2), 108.28 (C_7), 118.04 (C_5), 118.88 (C_1), 122.69 (C_6), 127.81 (C_{8a}), 127.95 (C_8), 132.01 (C_{4a}), 135.60 (C_{9a}), 137.90 (C_9), 159.68 and 163.90 (2CO).

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