COMMUNICATION

Efficient synthesis of functionalized 3*H*-pyrrolo[1,2-*a*]indoles

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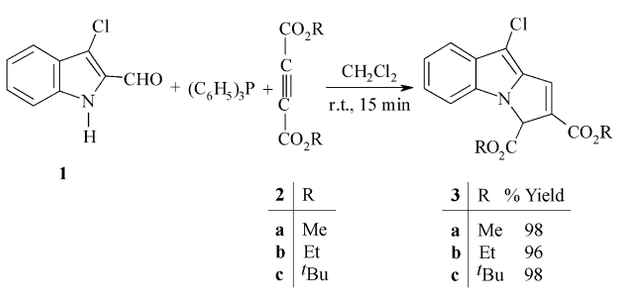
Dialkyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylates are obtained in excellent yields from the 1 : 1 : 1 addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates and 3-chloroindole-2-carbaldehyde; dimethyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate is converted to dimethyl 9-oxo-9*H*-pyrrolo-[1,2-*a*]indole-2,3-dicarboxylate.

Introduction

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.[1–4] The interest in tricyclic-fused 5:5:6 systems with one ring junction nitrogen atom between the five-membered rings and no extra heteroatoms, stems from the appearance of saturated and partially saturated annelated[*a*]indole ring systems in many biologically active compounds. Consequently, there has been an ongoing interest in the synthesis of pyrrolo[1,2-*a*]indole ring structures, especially synthesis of 2,3,9,9a-tetrahydro-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole, the "mitosane", basic skeleton of mitomycins.[3–7] With the purpose to prepare pyrrolo[1,2-*a*]-indole derivatives, we now report the reaction of 3-chloroindole-2-carbaldehyde **1** and dialkyl acetylenedicarboxylates **2** in the presence of triphenylphosphine.

Results and discussion

The reaction of 3-chloroindole-2-carbaldehyde **1** with acetylenic esters **2** in the presence of triphenylphosphine proceeds smoothly in dichloromethane at ambient temperature to produce dialkyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylates **3** in excellent yields (Scheme 1).



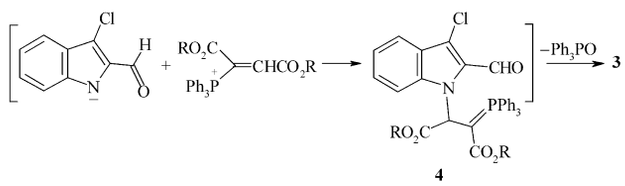
2	R
a	Me
b	Et
c	^{t}Bu

3	R	% Yield
a	Me	98
b	Et	96
c	^{t}Bu	98

Scheme 1

On the basis of the chemistry of trivalent phosphorus nucleophiles,[8–12] it is reasonable to assume that compound **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1 : 1 adduct by the NH-acid **1**. Then the positively charged ion is attacked by the nitrogen atom of the conjugate base of the NH-acid to form phosphorane **4**, which undergoes an intramolecular Wittig reaction to produce 3*H*-pyrrolo[1,2-*a*]indole derivatives **3** (Scheme 2).

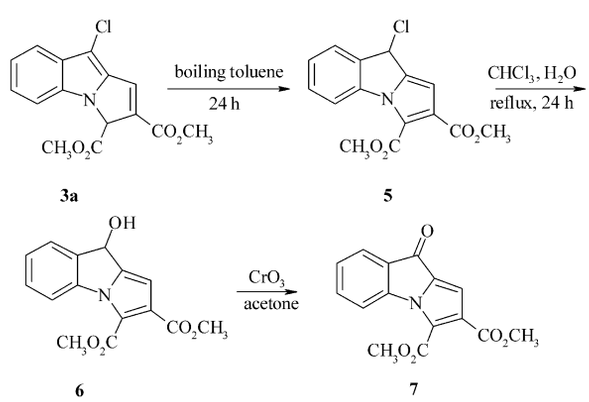
Structure **3** was assigned to the isolated products on the basis of their elemental analyses and their high-field ^{1}H and ^{13}C NMR and IR spectral data. The mass spectra of these



Scheme 2

compounds displayed molecular ion peaks at *m*/*z* = 305, 333 and 389, respectively. The ^{1}H NMR spectrum of compound **3a** exhibits two single sharp lines for the methoxy (δ = 3.78 and 3.87 ppm) protons. The two non-aromatic methine protons appear as two doublets at δ = 5.57 and 7.65 ppm with allylic coupling of $^4J_{HH}$ = 1.9 Hz. The ^{13}C NMR spectrum of **3a** exhibits a signal at δ = 63.75 ppm for the N–CH moiety. The ^{1}H and ^{13}C NMR spectra of **3b** and **3c** are similar to those of **3a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts.

When compound **3a** was refluxed in boiling toluene for 24 h, the ^{1}H NMR spectrum of the reaction mixture showed quantitative conversion to dimethyl 9-chloro-9*H*-pyrrolo[1,2-*a*]-indole-2,3-dicarboxylate (**5**). Compound **5** was quantitatively hydrolyzed to dimethyl 9-hydroxy-9*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (**6**) by refluxing in a mixture of chloroform and water for 24 h. Alcohol **6** was oxidized by chromium trioxide to dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (**7**) in quantitative yield (Scheme 3).



Scheme 3

Structures **5**–**7** were assigned on the basis of their elemental analyses and their ^{1}H NMR, ^{13}C NMR, and IR spectral data.

NMR spectroscopy was used to distinguish structure **5** from the primary product **3a**. Thus the ^{1}H NMR spectrum of compound **5** exhibited two singlets at δ = 5.85 and 6.77 ppm which, are readily assignable to the protons of the pyrrolizine moiety. These peaks are fairly broad as a result of very weak allylic couplings. These signals along with two sharp lines at 3.86 and 3.99 and the fairly complex multiplets of the phenylene moiety confirm the proposed structure. The ^{13}C NMR spectrum of compound **5** exhibited a signal at 49.17 ppm for the CH–Cl moiety.

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IR spectroscopy was applied to identify the hydrolysis product **6**. Thus, the IR spectrum of **6** showed a strong OH stretching band at about 3425 cm^{-1}. The ^1H NMR spectrum of **6** exhibited two doublets at 3.06 and 5.58 ppm ($^3J_{HH}$ = 9.7 Hz). The doublet at 3.06 arising from the OH group was eliminated after addition of D_2O. The ^{13}C NMR spectrum of **6** exhibited a signal at 67.12 for the CH–OH moiety.

The ^{13}C NMR spectrum of **7** exhibited a signal at 179.27 ppm for the carbonyl group. Partial assignments of ^1H and ^{13}C resonances in the ^1H and ^{13}C NMR spectra of compounds **5**–**7** are given in the Experimental section.

We anticipate that the reactions described here present a simple entry into the synthesis of polyfunctional pyrrolo-[1,2-*a*]indole derivatives of potential interest. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches.

Experimental

Dialkyl acetylenedicarboxylates and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. 3-Chloroindole-2-carbaldehyde was prepared by a known method.[13] 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. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

General procedure for preparation of compounds 3a–c

Dimethyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (3a). The typical process for the preparation of dimethyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (**3a**) is described as an example. To a magnetically stirred solution of 0.524 g triphenylphosphine (2 mmol) and 0.359 g 3-chloroindole-2-carbaldehyde **3** (2 mmol) in 6 mL dichloromethane was added dropwise a mixture of 0.284 g dimethyl acetylenedicarboxylate (2 mmol) in 2 mL dichloromethane at −5 °C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 15 min. The solvent was removed under reduced pressure and the product was extracted from the solid residue with 4 × 20 mL *n*-hexane. The solvent was removed under reduced pressure and the product was recrystallized from *n*-hexane–ethyl acetate (1 : 1) as yellow crystals, mp 136–139 °C, yield 0.6 g, 98%. IR (KBr) (ν_{max}/cm^{-1}): 1731 and 1693 (C=O). MS, *m*/*z* (%): 305 (M^+, 45), 290 (10), 270 (5), 246 (100), 216 (8), 187 (20), 152 (12). Anal. Calcd for $C_{15}H_{12}NO_4Cl$ (305.72): C, 58.93; H, 3.96; N, 4.58. Found: C, 58.9; H, 4.0; N, 4.6%. ^1H NMR: δ 3.78 and 3.87 (6 H, 2 s, 2 OCH_3), 5.57 (1 H, d, ^4J = 1.9 Hz, CH), 7.18 (1 H, t, J = 8.0 Hz, CH), 7.29 (1 H, t, J = 7.9 Hz, CH), 7.35 (1 H, d, J = 8.2 Hz, CH), 7.64 (1 H, t, J = 8.1 Hz, CH), 7.65 (1 H, d, ^4J = 1.9 Hz, CH). ^{13}C NMR: δ 52.23 and 53.28 (2 OCH_3), 63.75 (CH), 101.60 (C), 110.03, 120.10, 120.97, and 125.07 (4 CH), 129.79 (C), 130.89 (CH), 133.94, 134.57 and 139.34 (3 C), 162.58 and 167.11 (2 C=O).

Diethyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (3b). Yellow crystals, mp 87–88 °C (from *n*-hexane–ethyl acetate 1 : 1), yield 0.64 g, 96%. IR (KBr) (ν_{max}/cm^{-1}): 1731 and 1693 (C=O). MS, *m*/*z* (%): 333 (M^+, 27), 298 (10), 260 (100), 232 (60), 188 (20), 152 (12). Anal. Calcd for $C_{17}H_{16}NO_4Cl$ (333.77): C, 61.18; H, 4.83; N, 4.20. Found: C, 61.2; H, 4.8; N, 4.2%. ^1H NMR: δ 1.25 and 1.35 (6 H, 2 t, J = 7.1 Hz, 2 OCH_2CH_3), 4.23 (2 H, AMX$_3$ system, ^2J = 10.8 Hz and ^3J = 7.1 Hz, OCH_2CH_3), 4.31 (2 H, m, ABX$_3$ system, OCH_2CH_3), 5.51 (1 H, d, ^4J = 1.4 Hz, CH), 7.16 (1 H, t, J = 7.7 Hz, CH), 7.28 (1 H, t, J = 7.7 Hz, CH), 7.34 (1 H, d, J = 7.7 Hz, CH), 7.62 (1 H, t, J = 7.7 Hz, CH), 7.63 (1 H, d, ^4J = 1.4 Hz, CH). ^{13}C NMR: δ 14.08 and 14.25 (2 OCH_2CH_3), 61.20 and 62.48 (2 OCH_2CH_3), 64.01 (CH), 101.21 (C), 110.06, 119.99, 120.86, and 124.85 (4 CH), 129.76 (C), 130.53 (CH), 133.88, 135.18, and 139.46 (3 C), 162.14 and 166.60 (2 C=O).

Di-*tert*-butyl 9-chloro-3*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (3c). Yellow crystals, mp 107–109 °C (from *n*-hexane), yield 0.76 g, 98%. IR (KBr) (ν_{max}/cm^{-1}): 1723 and 1695 (C=O). MS, *m*/*z* (%): 389 (M^+, 4), 288 (10), 232 (55), 188 (20), 57 (100), 41 (28). Anal. Calcd for $C_{21}H_{24}NO_4Cl$ (389.88): C, 64.69; H, 6.20; N, 3.59. Found: C, 64.7; H, 6.8; N, 3.6%. ^1H NMR: δ 1.42 and 1.56 [18 H, 2 s, 2 $OC(CH_3)_3$], 5.34 (1 H, d, ^4J = 1.7 Hz, CH), 7.16 (1 H, t, J = 8.0 Hz, CH), 7.27 (1 H, t, J = 8.0 Hz, CH), 7.37 (1 H, d, J = 8.0 Hz, CH), 7.52 (1 H, d, ^4J = 1.7 Hz, CH), 7.62 (1 H, d, J = 8.0 Hz, CH). ^{13}C NMR: δ 27.83 and 28.15 [2 $OC(CH_3)_3$], 65.38 (CH), 81.96 and 83.35 [2 $OC(CH_3)_3$], 100.34 (C), 110.04, 119.81, 120.63, 124.44, and 129.75 (5 CH), 129.74, 133.80, 137.37, and 139.74 (4 C), 161.45 and 165.65 (2 C=O).

Dimethyl 9-chloro-9*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (5)

0.30 g (1 mmol) of **3a** was refluxed in boiling toluene (10 mL) for 24 h. Then the solvent was removed under reduced pressure and the solid residue was recrystallized from *n*-hexane–ethyl acetate (1 : 1) as colorless crystals, mp 135–137 °C, yield 0.3 g, 99%. IR (KBr) (ν_{max}/cm^{-1}): 1714 (C=O). MS, *m*/*z* (%): 305 (M^+, 71), 274 (15), 270 (100), 246 (32), 187 (14), 152 (7). Anal. Calcd. for $C_{15}H_{12}NO_4Cl$ (305.72): C, 58.93; H, 3.96; N, 4.58. Found: C, 58.8; H, 4.0; N, 4.5%. ^1H NMR: δ 3.86 and 3.99 (6 H, 2 s, 2 OCH_3), 5.85 (1 H, s, CH), 6.77 (1 H, s, CH), 7.27 (1 H, t, J = 7.6 Hz, CH), 7.40 (1 H, t, J = 7.8 Hz, CH), 7.56 (1 H, d, J = 7.5 Hz, CH), 7.83 (1 H, d, J = 8.1 Hz, CH). ^{13}C NMR: δ 49.17 (CH), 51.93 and 52.72 (2 OCH_3), 108.13 and 114.63 (2 CH), 120.97 and 124.21 (2 C), 126.26, 126.62, and 130.45 (3 CH), 136.34, 138.36, and 139.18 (3 C), 161.58 and 164.06 (2 C=O, ester).

Dimethyl 9-hydroxy-9*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (6)

0.30 g (1 mmol) of **5** was refluxed in a mixture of chloroform (10 mL) and water (2 mL) for 12 h. Then 20 mL chloroform was added. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the solid residue was recrystallized from *n*-hexane–ethyl acetate (1 : 2) as colorless crystals, mp 159–161 °C, yield 0.28 g, 99%. IR (KBr) (ν_{max}/cm^{-1}): 3425 (OH), 1709 and 1685 (C=O). MS, *m*/*z* (%): 287 (M^+, 82), 270 (100), 228 (15), 216 (17), 59 (6). Anal. Calcd for $C_{15}H_{13}NO_5$ (287.27): C, 62.72; H, 4.56; N, 4.88. Found: C, 62.8; H, 4.5; N, 4.9%. ^1H NMR: δ 3.06 (1 H, d, J = 9.7 Hz, OH), 3.72 and 3.93 (6 H, 2 s, 2 OCH_3), 5.58 (1 H, d, J = 9.7 Hz, OH) 6.65 (1 H, s, CH), 7.22 (1 H, t, J = 7.5 Hz, CH), 7.34 (1 H, t, J = 7.8 Hz, CH), 7.55 (1 H, d, J = 7.5 Hz, CH), 7.74 (1 H, d, J = 8.1 Hz, CH). ^{13}C NMR: δ 51.84 and 52.56 (2 OCH_3), 67.12 (CHOH), 107.42 and 114.36 (2 CH), 120.34 and 123.59 (2 C), 125.97, 126.02 and 129.87 (3 CH), 138.33, 139.29 and 140.97 (3 C), 161.72 and 164.51 (2 C=O, ester).

Dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-2,3-dicarboxylate (7)

0.28 g (1 mmol) of **6** and chromium trioxide 0.12 g was stirred in acetone (15 mL) at room temperature for 20 min. The solvent was evaporated and the product was extracted by diethyl ether. The organic layer was dried over anhydrous calcium chloride. The solvent was removed under reduced pressure and the solid residue was recrystallized from *n*-hexane–ethyl acetate (2 : 1) as yellow crystals, mp 157–159 °C. IR (KBr) (ν_{max}/cm^{-1}): 1699 (C=O). MS, *m*/*z* (%): 285 (M^+, 100), 257 (15), 226 (41), 187 (25), 142 (9), 79 (14), 59 (6). Anal. Calcd for $C_{15}H_{11}NO_5$ (285.27): C, 63.16; H, 3.89; N, 4.91. Found: C, 63.2; H, 3.9; N, 4.9%. ^1H NMR: δ 3.86 and 4.04 (6 H, 2 s, 2 OCH_3), 7.09 (1 H, s, CH), 7.26 (1 H, t, J = 7.5 Hz, CH), 7.51 (1 H, t, J = 7.9 Hz, CH), 7.57

(1 H, d, J = 7.9 Hz, CH), 7.65 (1 H, d, J = 7.5 Hz, CH). ^{13}C NMR: δ 52.06 and 53.27 (2 OCH_3), 113.21 and 114.38 (2 CH), 123.96 (C), 124.82 (CH), 126.39 (C), 127.16 (CH), 129.52 and 131.72 (2 C), 135.55 (CH), 143.49 (C), 161.11 and 162.93 (2 C=O, ester), 179.27 (C=O).

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