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An Efficient One-pot Synthesis of 4*H*-Pyrrolo[3,2,1-*ij*]quinolines

Mehdi Adib* and **Mohammad H. Sayahi**

Department of Chemistry, Faculty of Science, University of Tehran,
P.O. Box 14155-6455, Tehran, Iran

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Summary. Dialkyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylates are obtained in quantitative yields from the 1:1:1 addition reaction between triphenylphosphine, dialkyl acetylenedicarboxylates, and indole-7-carboxaldehyde.

Keywords. Indole-7-carboxaldehyde; Acetylenic esters; Intramolecular *Wittig* reaction; Triphenylphosphine; 4*H*-Pyrrolo[3,2,1-*ij*]quinolines.

Introduction

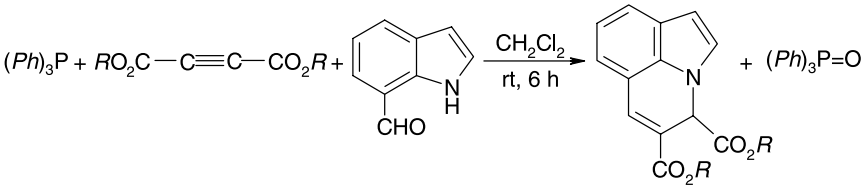
Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity [1]. The interest in tricyclic 5–6–6 systems with one ring junction nitrogen atom (between the five- and one of the six-membered rings) and no extra heteroatoms, stems from the appearance of saturated and partially saturated pyrrolo[3,2,1-*ij*]quinoline ring systems in many biologically active compounds. Derivatives containing the pyrrolo[3,2,1-*ij*]quinoline ring system (previously named benzo[*h*,*i*]indolizidine in literature) [2] have been shown to be the heterocyclic core of lilolidine alkaloids, which constitute active antihistamines, inhibitors of leukotriene synthesis, and antagonists of the platelet activating factor, both *in vitro* and *in vivo*, to possess antibacterial activity. In addition, these can be used to treat epilepsy, obesity, and allergic diseases, such as asthma and rhinitis [3–5]. Consequently, there has been an ongoing interest in the synthesis of pyrrolo[3,2,1-*ij*]quinoline ring structures [3–9]. As part of our current studies on the development of new routes in heterocyclic synthesis [10–15], in this paper we wish to report a facile and efficient synthesis of 4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives.

* Corresponding author. E-mail: madib@khayam.ut.ac.ir

Results and Discussion

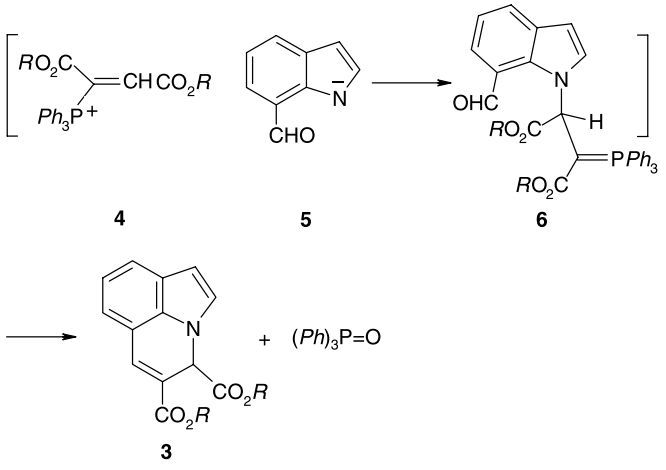
The reaction of acetylenic esters **1** with indole-7-carboxaldehyde (**2**) in the presence of triphenylphosphine proceeds smoothly in dichloromethane at ambient temperature to produce dialkyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylates **3** in quantitative yields (Scheme 1). The reactions were carried out by first mixing triphenylphosphine and **2**, and then the acetylenic ester **1** was added slowly. The reactions proceeded spontaneously in CH_2Cl_2, and were complete within a few hours. The ^1H and ^{13}C NMR spectra of the crude product clearly indicated the formation of dialkyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylates **3**. No other product than **3** and triphenylphosphine oxide could be detected by NMR spectroscopy.

Structures **3a**–**3d** were assigned on the basis of their elemental analyses, IR, high-field ^1H and ^{13}C NMR, and mass spectral data. The mass spectra of these compounds displayed molecular ion [M^+] peaks at $m/z = 271$, 299, 327, and 355. The ^1H NMR spectrum of **3a** exhibited two single sharp lines for the methoxy protons ($\delta = 3.77$ and 3.91 ppm), a sharp singlet for the methine proton ($\delta =$ 6.14 ppm), and a single sharp line for the vinylic proton ($\delta = 7.89$ ppm) along with characteristic multiplets with appropriate chemical shifts and coupling constants for the five aromatic protons.



	R			R
1a	*Me*	**2**	**3a**	*Me*
1b	*Et*		**3b**	*Et*
1c	*iPr*		**3c**	*iPr*
1d	*tBu*		**3d**	*tBu*

Scheme 1



Scheme 2

The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 15 distinct resonances in agreement with the structure of the product. The ^{1}H and ^{13}C NMR spectra of **3b**–**3d** are similar to those of **3a**, except for the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts and coupling constants.

On the basis of the chemistry of trivalent phosphorus nucleophiles [16] it is reasonable to assume that **3** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by the NH-acid **2**. Then the positively charged ion **4** is attacked by the nitrogen atom of the conjugate base of the NH-acid **5** to form the phosphorane **6**, which undergoes an intramolecular *Wittig* reaction to produce the 4*H*-pyrrolo[3,2,1-*ij*]quinoline derivative **3** (Scheme 2).

In conclusion, the present method has the advantage that, not only is the reaction performed under neutral conditions, but also the educts can be mixed without any activation or modification. The simplicity of the procedure makes it an interesting alternative to multistep approaches [3–9]. Thus, it provides an acceptable efficient one-pot method for the preparation of functionalized pyrrolo[3,2,1-*ij*]quinolines of potential synthetic and pharmaceutical interest.

Experimental

Acetylenedicarboxylates **1a**–**1d**, **2**, and triphenylphosphine were obtained from Merck (Germany), Fluka (Switzerland), and Acros (Belgium), and were used without further purification. 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. The obtained results values were within the limits of experimental error. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

*General Procedure (examplified by **3a**)*

To a magnetically stirred solution of 0.262 g triphenylphosphine (1 mmol) and 0.145 g **2** (1 mmol) in 5 cm^3 CH_2Cl_2 was added dropwise a solution of 0.142 g **1a** (1 mmol) in 2 cm^3 CH_2Cl_2 at $-5°C$ for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 6 h. The solvent was removed and the residue was purified by column chromatography using *n*-hexane: *Et*O*Ac* (4:1) as eluent and then the product crystallized from *n*-hexane: *Et*O*Ac* (1:1).

Dimethyl 4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (**3a**, $C_{15}H_{13}NO_4$)

Pale yellow crystals, mp 85–88°C, yield 0.27 g (99%); IR (KBr): $\bar{\nu} = 1745$ and 1695 (C=O), 1593, 1433, 1364, 1294, 1263, 1221, 1057, 1007, 918, 797, 721 cm^{-1}; ^{1}H NMR: $\delta = 3.77$ and 3.91 (2s, 2 OCH_3), 6.14 (s, NCH), 6.60 (d, $J = 3.1$ Hz, NCH=C*H*), 7.07 (dd, $J = 7.7$, 7.3 Hz, CH), 7.12 (d, $J = 7.3$ Hz, CH), 7.32 (d, $J = 3.1$ Hz, NC*H*=CH), 7.60 (d, $J = 7.7$ Hz, CH), 7.89 (s, CH) ppm; ^{13}C NMR: $\delta = 52.18$ and 52.96 (2 OCH_3), 58.17 (NCH), 103.84 (CH), 115.88 (C), 120.95 and 121.62 (2 CH), 121.64 (C), 124.54 (CH), 125.22 (C), 126.33 (CH), 133.36 (C), 134.83 (CH), 165.71 and 168.78 (2 C=O) ppm; MS: m/z (%) = 271 (M^+, 3), 212 (100), 182 (5), 153 (23), 126 (8), 59 (4).

Diethyl 4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (**3b**, $C_{17}H_{17}NO_4$)

Pale yellow crystals, mp 86–89°C, yield 0.29 g (99%); IR (KBr): $\bar{\nu} = 1734$ and 1690 (C=O), 1595, 1456, 1371, 1292, 1255, 1219, 1091, 1057, 1022, 919, 791, 733 cm^{-1}; ^{1}H NMR: $\delta = 1.30$ and 1.43 (2t, $J = 7.1$ Hz, 2 OCH_2CH_3), 4.21 and 4.27 (2dq, ABX_3 system, $J = 10.8$, 7.1 Hz, $OCH_AH_BCH_3$), 4.33–4.43 (m, OCH_2CH_3), 6.14 (s, NCH), 6.60 (d, $J = 3.1$ Hz, NCH=C*H*), 7.08 (dd, $J = 7.6$, 7.4 Hz,

CH), 7.14 (d, $J = 7.1$ Hz, CH), 7.34 (d, $J = 3.1$ Hz, NC*H*=CH), 7.61 (d, $J = 7.8$ Hz, CH), 7.91 (s, CH) ppm; ^{13}C NMR: $\delta = 14.02$ and 14.27 (2 OCH_2CH_3), 58.42 (NCH), 61.12 and 62.01 (2 OCH_2CH_3), 103.71 (CH), 116.00 (C), 120.88 and 121.48 (2 CH), 122.20 (C), 124.36 (CH), 125.18 (C), 126.23 (CH), 133.39 (C), 134.48 (CH), 165.30 and 168.29 (2 C=O) ppm; MS: m/z (%) = 299 (M^+,10), 226 (100), 198 (50), 182 (9), 154 (19), 116 (4), 96 (10), 57 (13), 29 (30).

Diisopropyl 4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (**3c**, $C_{19}H_{21}NO_4$)
Pale yellow crystals, mp 48–50°C, yield 0.32 g (99%); IR (KBr): $\bar{\nu} = 1740$ and 1709 (C=O), 1639, 1599, 1460, 1362, 1250, 1219, 1200, 1111, 793, 729 cm^{-1}; ^{1}H NMR: $\delta = 1.30$ (d, $J = 6.3$ Hz, $OCH(CH_3)_2$), 1.41 and 1.42 (2d, $J = 6.3$ Hz, $OCH(CH_3)_2$), 5.08 and 5.25 (2septet, $J = 6.3$ Hz, 2 $OCH(CH_3)_2$), 6.14 (s, NCH), 6.61 (d, $J = 3.1$ Hz, NCH=C*H*), 7.09 (t, $J = 7.5$ Hz, CH), 7.16 (d, $J = 7.1$ Hz, CH), 7.36 (d, $J = 3.1$ Hz, NC*H*=CH), 7.62 (d, $J = 7.8$ Hz, CH), 7.92 (s, CH) ppm; ^{13}C NMR: $\delta = 21.52$, 21.58, 21.78, and 21.90 (2 $OCH(CH_3)_2$), 58.59 (NCH), 68.65 and 69.81 (2 $OCH(CH_3)_2$), 103.55 (CH), 116.07 (C), 120.77 and 121.30 (2 CH), 122.68 (C), 124.16 (CH), 125.09 (C), 126.10 (CH), 133.37 (C), 134.19 (CH), 164.80 and 167.76 (2 C=O) ppm; MS: m/z (%) = 327 (M^+, 50), 284 (20), 267 (19), 240 (98), 225 (38), 198 (100), 152 (75), 126 (15), 77 (5), 43 (43).

Ditertbutyl 4H-pyrrolo[3,2,1-ij]quinoline-4,5-dicarboxylate (**3d**, $C_{21}H_{25}NO_4$)
Pale yellow crystals, mp 95–98°C, yield 0.35 g (99%); IR (KBr): $\bar{\nu} = 1734$ and 1709 (C=O), 1641, 1601, 1483, 1366, 1251, 1221, 1159, 1047, 847, 793, 725 cm^{-1}; ^{1}H NMR: $\delta = 1.48$ and 1.64 (2s, 2 $OC(CH_3)_3$), 6.02 (s, NCH), 6.59 (d, $J = 3.1$ Hz, NCH=C*H*), 7.07 (t, $J = 7.5$ Hz, CH), 7.12 (d, $J = 7.0$ Hz, CH), 7.35 (d, $J = 3.1$ Hz, NC*H*=CH), 7.59 (d, $J = 7.8$ Hz, CH), 7.82 (s, CH) ppm; ^{13}C NMR: $\delta = 27.82$ and 28.16 (2 $OC(CH_3)_3$), 59.52 (NCH), 81.47 and 82.62 (2 $OC(CH_3)_3$), 103.40 (CH), 116.34 (C), 120.71, 121.05, and 123.90 (3 CH), 124.24 and 125.08 (2 C), 126.11 and 133.41 (2 CH), 133.44 (C), 164.53 and 167.44 (2 C=O) ppm; MS: m/z (%) = 355 (M^+, 1), 277 (3), 254 (15), 198 (100), 152 (13), 77 (4), 57 (72), 41 (24).

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