

One pot synthesis of pyridophenanthroline and pyrrolophenanthroline derivatives by regioselective reaction between 1,7-phenanthroline and dialkyl acetylenedicarboxylate: new fused heterocyclic compounds

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1,7-Phenanthroline reacts with dialkyl acetylenedicarboxylate in a regioselective manner to give new macromolecules such as tetramethyl-6a *H*-pyrido[1,2-*i*][1,7]phenanthroline-7,8,9,10-tetracarboxylate and trialkyl pyrrolo[1,2-*i*][1,7]phenanthroline-7,8,9-tricarboxylate derivatives.

Key Words: 1,7-Phenanthroline, tetramethyl-6a *H*-pyrido[1,2-*i*][1,7]phenanthroline-7,8,9,10-tetracarboxylate, trialkyl pyrrolo[1,2-*i*][1,7]phenanthroline-7,8,9-tricarboxylate derivatives, regioselective cycloaddition reaction

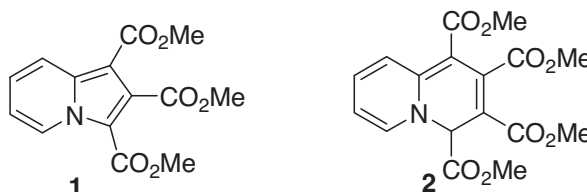
Introduction

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic chemistry.¹ Bridgehead nitrogen heterocycles have been the subject of great

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consideration because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activity.²⁻⁴ For example, the esters of pyrrole-2-carboxylic acids have been extensively utilized as intermediates in the total synthesis of porphyrins.⁵

These valuable intermediates are commonly prepared by variations of the Knorr pyrrole condensation,^{5,6} although several other routes have been recently developed for these systems.⁷⁻¹¹ The interesting reaction between pyridine and dimethyl acetylenedicarboxylate typically produces indolizine-1,2,3-tricarboxylate **1** or 4*H*-quinolizine **2** (Scheme 1).^{3,4,12-25}



Scheme 1.

Indolizine is an important ring system with 10 delocalized π -electrons that confer aromaticity, in contrast to its analogs, pyrrolizine and quinolizine. Consequently, it has theoretical and practical interest. Apart from academic interest in its synthesis and properties, most of the work on indolizine has been concerned with the search for drugs, dyestuffs, and light screening agents in photographic emulsions.³

We recently reported another 2-component condensation between [1,10]phenanthroline and dialkyl acetylenedicarboxylate for preparation of helical dipyrrolophenanthrolines.²³⁻²⁵ Herein we describe the synthesis of new compounds **5** and **6** derived from the reaction between dialkyl acetylenedicarboxylate and 1,7-phenanthroline in different reaction conditions.¹²⁻²⁰

Experimental

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and Shimadzu IR-470 spectrometer, respectively. ¹H- and ¹³C-NMR spectra were obtained from Bruker DRX 500 and 300 Avance instruments with CDCl₃ as the solvent at 500.1 and 125.7 MHz for **5** and 300 and 75 MHz for **6**, respectively. In addition, elemental analysis of C, H, and N was performed using a Heraeus CHN-O-rapid analyzer, and mass spectra were recorded on a Finnigan MAT-8430 mass spectrometer operating at an ionization potential of 70 eV. Dialkyl acetylenedicarboxylate and 1,7-phenanthroline were obtained from Fluka and used without further purification.

Typical procedure for preparation of compound **5**

To a magnetically stirred solution of 1,7-phenanthroline (0.18 g, 1 mmol) in 10 mL of dry CH₃CN, a mixture of dimethyl acetylenedicarboxylate (0.31 g, 2.2 mmol) in CH₃CN (2 mL) was added dropwise at room temperature over the course of 5 min, and the mixture was refluxed for 10 h. The solvent was then allowed to stand for at least 5 days. After that time, the solvent was removed under reduced pressure, the solid residue was washed by cold diethyl ether (2 × 3 mL), and product **5** was obtained as a brown powder (0.21 g, yield 45%), mp

208-210 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1740, 1713, and 1680 (C=O), 1230 and 1190 (C-O). $^1\text{H-NMR}$ (500.1 MHz, CDCl_3): δ = 3.55, 3.66, 3.73, and 3.90 (12H, 4s, 4 OMe), 5.23 (1H, t, J = 7.0 Hz, C-6_a-H), 6.17 (1H, dd, J_1 = 9.4 J_2 = 3.0 Hz, C-6-H), 7.39 (1H, d, J = 8.8 Hz, C-12-H), 7.44 (1H, dd, J_1 = 8.3, J_2 = 4.1 Hz, C-2-H), 7.68 (1H, d, J = 8.8 Hz, C-11-H), 7.77 (1H, dd, J_1 = 9.4, J_2 = 2.46 Hz, C-5-H), 8.12 (1H, dd, J_1 = 8.3, J_2 = 1.6 Hz, C-1-H), 8.94 (1H, dd, J_1 = 4.1, J_2 = 1.6 Hz, C-3-H). $^{13}\text{C-NMR}$ (125.7 MHz, CDCl_3): δ = 52.05, 52.33, 52.56, and 52.89 (4 OMe), 54.30 (C-6_a), 98.33, 112.37, 120.77, 121.76, 121.79, 127.17, 127.21, 128.10, 130.33, 136.20, 136.42, 138.22, 143.79, 150.63, and 151.16 (15 C), 162.79, 163.63, 163.79, and 167.48 (4 CO). MS (m/z , %): 464 (M^+ , 36), 405 (100), 345 (18), 288 (18), 229 (19). Anal. Calcd. for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_8$ (464.42): C, 62.06; H, 4.31; N, 6.03. Found: C, 62.36; H, 4.08; N, 6.53.

Preparation of product 6a

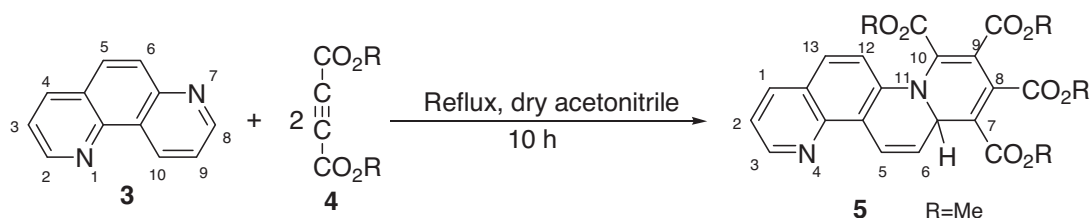
This product was prepared similar to **5** by replacing methanol as the solvent. The product was a brown powder (0.1 g, yield 50%), mp 197-199 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1741 and 1698 (C=O), 1211 and 1170 (C-O). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 3.97, 4.00, and 4.04 (9H, 3s, 3 OMe), 7.60 (1H, dd, J_1 = 8.1, J_2 = 4.3 Hz, C-2-H), 7.95 (1H, d, J = 9.4 Hz, C-12-H), 8.18 (1H, d, J_1 = 9.4 Hz, C-11-H), 8.3 (1H, dd, J_1 = 8.1 J_2 = 1.5 Hz, C-1-H), 8.50 (1H, d, J_1 = 9.6 Hz, C-6-H), 9.09 (1H, dd, J_1 = 4.3, J_2 = 1.5 Hz, C-3-H), 9.23 (1H, d, J_1 = 9.6 Hz, C-5-H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 51.92, 52.57, and 52.94 (3 OMe), 117.05, 118.80, 120.42, 122.13, 124.36, 125.65, 127.59, 132.55, 133.65, 137.83, 138.68, 149.26, 161.05, 163.14, and 166.01 (15 C), 161.05, 163.14, and 166.01 (3 C=O). MS (m/z , %): 392 (M^+ , 100), 361 (53), 334 (6), 303 (38), 289 (62), 259 (15), 244 (32), 216 (61), 179 (20).

Selected data for product 6b

Brown powder (0.1 g, yield 50%), mp 197-199 °C, IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1725 and 1690 (C=O), 1210 and 1198 (C-O). $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 1.42-1.50 (9H, m, 3 CH_3), 4.40-4.53 (6H, m, 3 CH_2), 7.65 (1H, dd, J_1 = 8.1, J_2 = 4.3 Hz, C-2-H), 7.98 (1H, d, J = 9.4 Hz, C-12-H), 8.24 (1H, d, J = 9.4 Hz, C-11-H), 8.37 (1H, d, J = 8.1 Hz, C-1-H), 8.58 (1H, d, J = 9.57 Hz, C-6-H), 9.13 (1H, dd, J_1 = 4.3, J_2 = 1.5 Hz, C-3-H), 9.30 (1H, d, J = 9.57 Hz, C-5-H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ = 14.04, 14.10, 14.33 (3 CH_3), 60.55, 61.70, 61.84 (3 CH_2), 104.92, 116.95, 118.30, 119.89, 122.02, 122.72, 124.32, 125.30, 127.45, 132.27, 133.26, 136.39, 138.78, 144.36, and 150.08 (15 C), 160.72, 162.83, and 165.57 (3 C=O). MS (m/z , %): 434 (M^+ , 100), 389 (16), 362 (18), 317 (42), 289 (28), 271 (43), 262 (15), 245 (18), 216 (39), 179 (21).

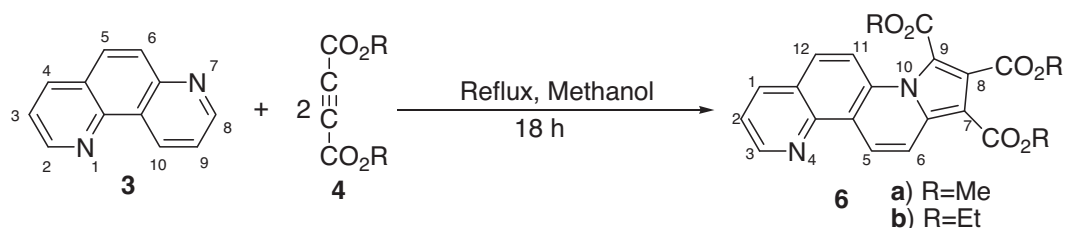
Results and discussion

We found that 1,7-phenanthroline undergoes a smooth reaction with dimethyl acetylenedicarboxylate in acetonitrile to give the hitherto unknown tetramethyl-6aH pyrido[1,2-*i*][1,7]phenanthroline-7,8,9,10-tetracarboxylate (**5**) in moderate yield (Scheme 2).



Scheme 2.

We also succeeded in obtaining the primary cycloadducts, trialkylpyrrolo[1,2-*i*][1,7]phenanthroline-7,8,9-tricarboxylate (**6**) derivatives, by replacing the aprotic solvent used in the reaction with methanol as a protic solvent (Scheme 3).

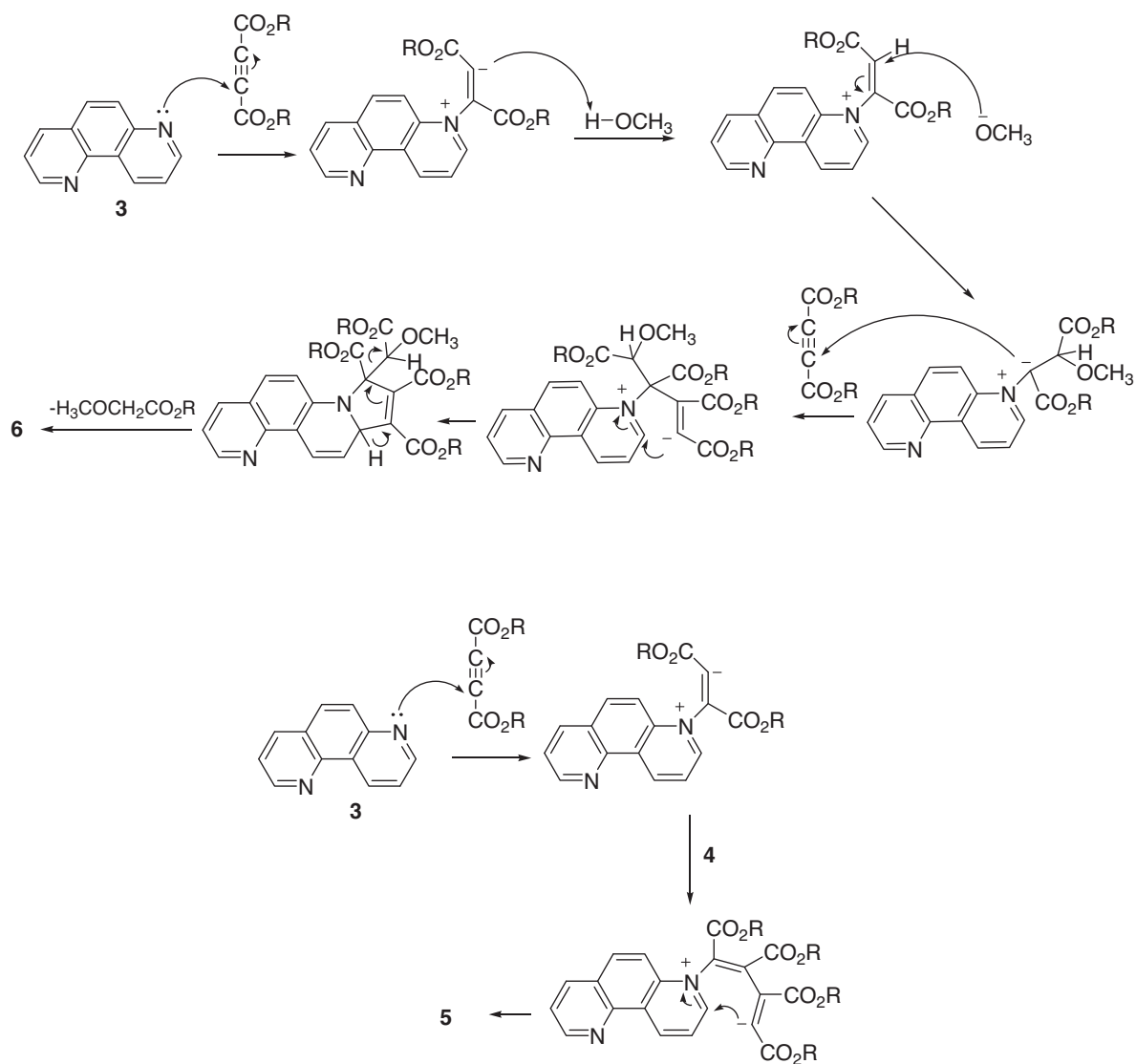


Scheme 3.

The structures of compounds **5** and **6** were deduced from their elemental analyses, ¹H- and ¹³C-NMR spectra, and IR spectra, which exhibited strong signals for C=O. The mass spectra of these compounds displayed a molecular ion peak at appropriate *m/z* values. Any initial fragmentation involved loss of the ester moieties. The ¹H-NMR spectrum of compound **5** exhibited 4 sharp lines arising from 4 methoxy protons (δ 3.55, 3.66, 3.73, and 3.90) and 8 distinct resonances of other recognizable protons (δ 5.23, 6.17, 7.39, 7.44, 7.68, 7.77, 8.12, and 8.94). The ¹³C-NMR spectrum of **5** displayed 4 signals (δ 52.05, 52.33, 52.56, and 52.89) for the methoxy groups. The chemical shifts of the ester carbonyl groups at δ 162.79, 163.63, 163.79, and 167.48 were consistent with the structure of **5** (see experimental section).

The ¹H-NMR spectrum of **6a**, in comparison with the 1,7-phenanthroline reactant, exhibited a doublet of a doublet peak for C-1-H. For this reason, it is clear that the proton in the position of C-3 (C-3-H in **6a**) was not omitted during the process of reaction. With respect to the above observation, an additional reason could be mentioned from the experimental data. The C-5-H of **6a** appeared as a doublet, which indicates that the C-8-H of 1,7-phenanthroline (reactant) would be removed (See Figure).

In addition, in **6b**, the ¹H-NMR spectrum of the methylene groups exhibited only 3 quartets; this observation is strong proof that **6b** could not be a chiral compound. Thus, the cyclization process occurred on position 4 of **6b** (N-4). If the reaction was processed from position 1 of 1,7-phenanthroline, the product would be obtained as a chiral compound and the methylene groups would appear as 4 separate quartets in the ¹H-NMR spectrum.²⁶ The above observation can be employed in the same manner for **5**, but the cyclization process would proceed from position 7 of 1,7-phenanthroline (N-7).



Scheme 4.

Illustrative mechanisms for the generation of compounds 5 and 6 are shown in (Scheme 4).^{12,14,25}

Briefly, we developed an efficient synthetic method for the preparation of tetramethyl-6a*H*-pyrido[1,2-*i*][1,7]phenanthroline-7,8,9,10-tetracarboxylate and trialkyl pyrrolo[1,2-*i*][1,7]phenanthroline-7,8,9-tricarboxylate derivatives. The present reactions were performed under neutral conditions, and the starting materials can react without any prior activation.

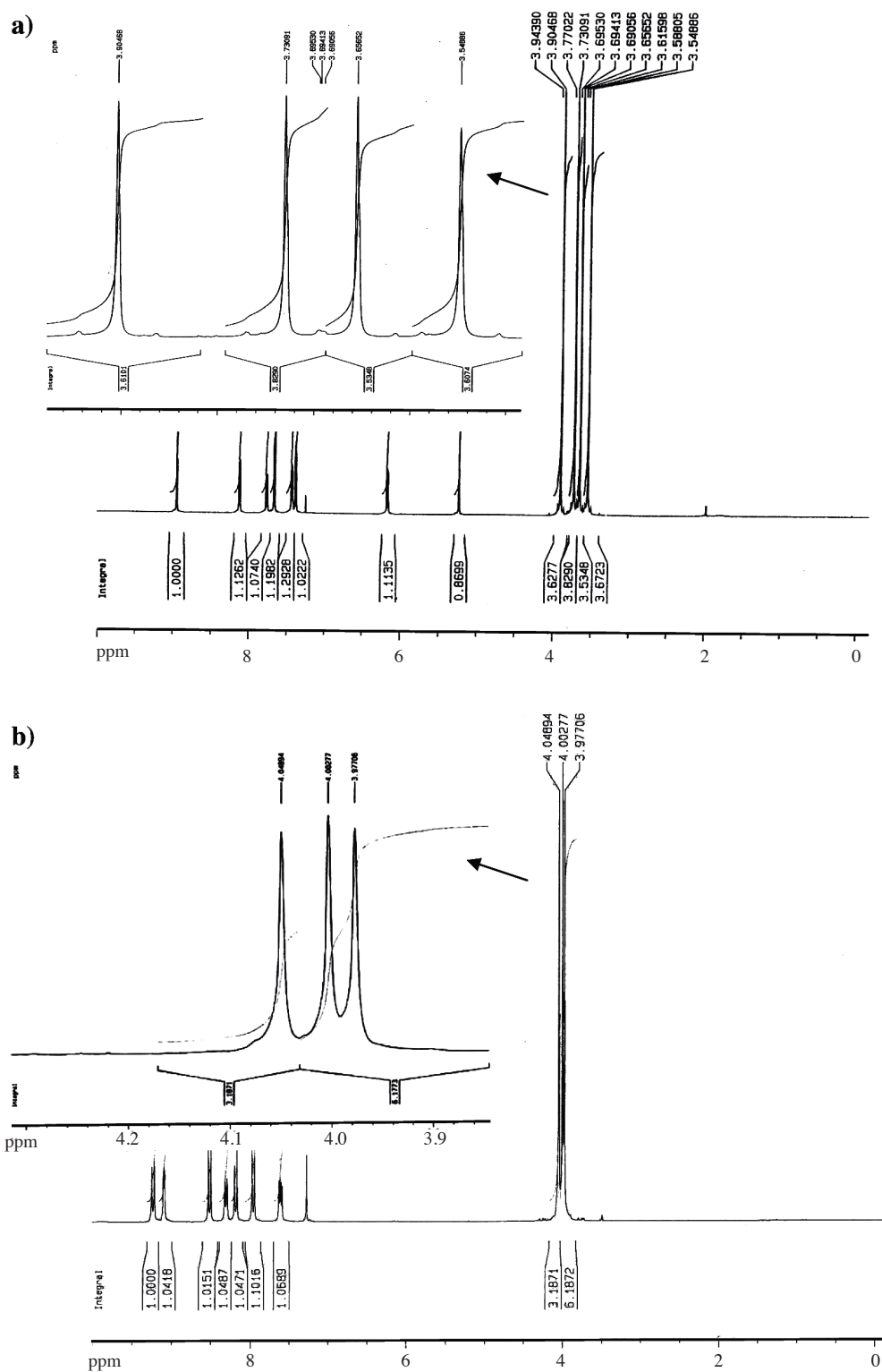


Figure. The methoxy signals in the $^1\text{H-NMR}$ spectra of a) compound **5** and b) compound **6a**.

Acknowledgements

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