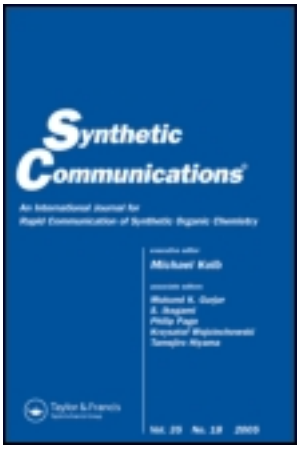

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Synthesis of Functionalized Pyrido[1,2-f]phenanthridines from Phenanthridine, Activated Acetylenes, and Arylidenemalononitriles

Hossein Mehrabi [a] & Mahdi Hatami-pour [a]

[a] Department of Chemistry, Rafsanjan Vali-e-Asr University, Rafsanjan, Iran

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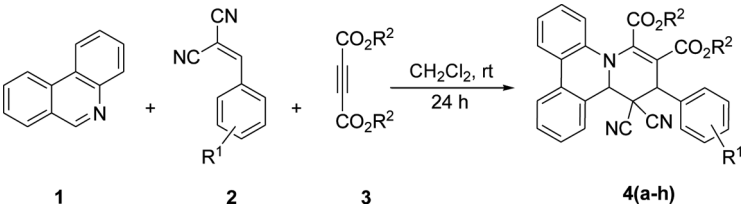
SYNTHESIS OF FUNCTIONALIZED PYRIDO[1,2-*f*]PHENANTHRIDINES FROM PHENANTHRIDINE, ACTIVATED ACETYLENES, AND ARYLIDENEMALONONITRILES

Hossein Mehrabi and Mahdi Hatami-pour
Department of Chemistry, Rafsanjan Vali-e-Asr University, Rafsanjan, Iran

GRAPHICAL ABSTRACT



Abstract *The zwitterions generated from phenanthiridine and dialkyl acetylenedicarboxylates (DAADs) react with a variety of arylidenemalononitriles, affording substituted pyrido[1,2-*f*]phenanthridines.*

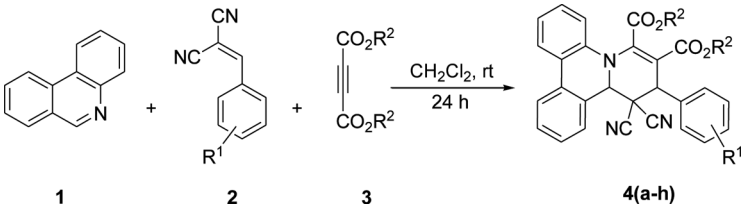
Keywords Arylidenemalononitrile; dialkyl acetylenedicarboxylate; phenanthridine; pyrido[12-*f*]phenanthridine derivatives; three-component reaction

INTRODUCTION

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more important.[1] Phenanthridine derivatives have attracted considerable attention in medicinal chemistry and in material science because of their biological activity and their presence in a variety of significant natural products and synthetic dyestuffs.[2] The development of new, efficient methods to synthesize N-heterocycles with structural diversity is one major interest of modern synthetic organic chemists.[3]

1,4-Dipolar cycloaddition provides an efficient and convenient route for the synthesis of six-membered heterocyclic compounds. However, these reactions have received only scant attention when compared to the related 1,3-dipolar cycloaddition

Received February 22, 2011.
Address correspondence to Hossein Mehrabi, Department of Chemistry, Rafsanjan Vali-e-Asr University, Rafsanjan 77176, Iran. E-mail: mehraby_h@yahoo.com



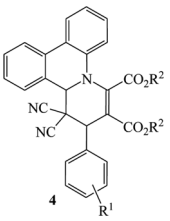
Scheme 1. Reaction of phenanthridine, dialkyl acetylenedicarboxylates, and arylidenemalononitriles.

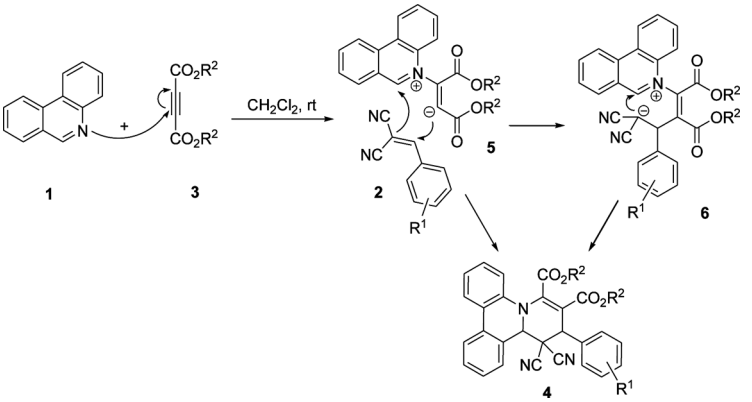
reactions. Extensive work has been done on the reactivities of 1,4-dipoles derived from dimethyl acetylenedicarboxylate (DMAD) and nucleophiles such as phosphines,[4] isocyanides,[5] dimethoxycarbene,[6] nitrogen heterocycles,[7] and nucleophilic heterocyclic carbenes (NHC).[8] These studies have led to a number of interesting carbon–carbon bond-forming reactions and heterocyclic constructions.[9] The addition of quinoline–DMAD zwitterion to aldehydes, diaryl 1,2-diones, and arylidenemalononitriles has also been reported to afford three-component addition products.[10]

To the best of our knowledge, there has not been any report on the reaction between phenantridine and activated acetylenes in the presence of arylidenemalononitriles. We herein report a hitherto unknown three-component reaction of phenantridine, dialkyl acetylenedicarboxylates (DAADs), and arylidenemalononitriles after stirring in dry dichloromethane for 24 h to afford substituted pyrido[1,2-*f*]phenanthridines (Scheme 1, Table 1).

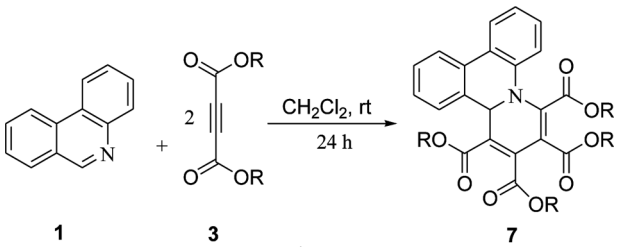
The structures of the products **4a–h** were deduced from their elemental analyses, infrared (IR), ^{1}H NMR, and ^{13}C NMR spectra. For example, in the ^{1}H NMR spectrum of **4c**, signals due to the methoxy carbonyl protons were observed as sharp singlets at δ 3.57 and 3.82 ppm. The two methine protons were discernible as two single signals at δ 5.10 and 5.88 ppm. The aromatic protons resonated in the region δ 6.97–8.16 ppm. The ^{13}C NMR spectrum of compound **4c** exhibited 27 distinct signals, in agreement with the proposed structure. In the IR spectrum, the ester carbonyl absorptions were observed at 1743 and 1716 cm^{-1} and 2364 cm^{-1} for cyanide groups. Also, the ^{1}H and ^{13}C NMR spectra of the other compounds **4a–h** were similar to those of **4c**, except for the aromatic moiety and the ester groups, which exhibited characteristic signals with appropriate chemical shifts.

Table 1. Reaction of phenantridine, dialkyl acetylenedicarboxylates, and arylidenemalononitriles

4	R^1	R^2	Product
a	4-Br	Et	
b	4-F	Et	
c	4-Br	Me	
d	4-Cl	Me	
e	4-Cl	Et	
f	2,4-Cl_2	Me	
g	3-NO_2	Me	
H	4-NO_2	Me	



Scheme 2. Suggested mechanism for formation of compounds **4**.



7	R	Yield (%)
a	Et	50
b	Me	53

Scheme 3. Reaction between phenanthridine and dialkyl acetylenedicarboxylates.

In the absence of any theoretical studies, the mechanistic details of the reaction are not fully understood. The initial event is the formation of dipolar species **5** from phenanthiridin and dialkyl acetylenedicarboxylates. Reaction of 1,4-dipolar cycloaddition of **5** with the electrophilic C=C of the arylidenemalononitriles affords pyrido[1,2-*f*]phenanthridines. Alternatively, the reaction may take place in two steps. The zwitterion **5** may add to the arylidenemalononitriles to form the intermediate **6**, which then undergoes cyclization to give the products **4** (Scheme 2).

We also investigate the reaction between phenantridine and dialkyl acetylenedicarboxylates. After stirring the reaction mixture in dichloromethane for 24 h and column chromatography, compounds **7** were obtained in 50–53% yields (Scheme 3).

In summary we report herein a simple route for the synthesis of substituted pyrido[1,2-*f*]phenanthridines by one-pot, three-component reaction of phenantridine, dialkyl acetylenedicarboxylates, and arylidenemalononitriles. Not only is the reaction performed under neutral conditions, but also the substances can be mixed without any modification or purification.

EXPERIMENTAL

The chemicals used in this work were purchased from Merck and Aldrich chemical companies. Melting points were determined using a Mettler FP5 apparatus and are uncorrected. IR spectra were determined using KBr pellets on a Shimadzu recording spectrophotometer, model 435. ^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker 400 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed using a Carlo Erba EA 1108 instrument.

Representative Experimental Procedure

Diethyl acetylenedicarboxylate (82.51 mg, 0.50 mmol) in dry dichloromethane (5 mL) was added dropwise to a mixture of 2-(4-bromobenzylidene)malononitrile **2a** (116.0 mg, 0.50 mmol) and phenanthridine (89.5 mg, 0.50 mmol) in dry dichloromethane (10 mL) at room temperature. The reaction mixture was stirred for a further 24 h. Removal of the solvent followed by purification of the reaction mixture by column chromatography (silica gel, 100–200 mesh; 90:10 n-hexane / ethyl acetate) afforded **4a** as a yellow solid, which could be recrystallized from ethyl acetate / hexane (1:1).

Diethyl-8-(4-bromophenyl)-9,9-dicyano-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4a)

Yield = 198 mg, 34%. Mp = 260–262 °C. IR (KBr) υ_{max}: 3077, 2980, 2364, 1738, 1694, 1589, 1490, 1267, 1122, 728 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.13$ (d, $j = 7.6$ Hz, 1H), 8.01 (d, $j = 7.6$ Hz, 1H), 7.67 (d, $j = 8$ Hz, 2H), 7.60 (dd, $j = 7.6$ Hz, 2H), 7.53 (d, $j = 7.6$ Hz, 1H), 7.33 (dd, $j = 8$ Hz, 3H), 7.13 (dd, $j = 7.6$ Hz, 1H), 6.97 (d, $j = 7.6$ Hz, 1H), 5.88 (s, 1H), 5.09 (s, 1H), 4.36 (q, $j = 7.2$, 1H), 4.22 (q, $j = 7.2$, 1H), 3.98 (q, $j = 7.2$, 2H), 1.22 (t, $j = 7.2$, 3H), 0.98 (t, $j = 7.2$, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.4$, 163.7, 142.7, 137.9, 135.0, 132.2, 131.1, 130.5, 130.4, 129.3, 128.7, 126.0, 124.9, 124.0, 123.5, 122.9, 122.6, 122.3, 117.0, 113.9, 112.1, 62.9, 61.9, 61.6, 50.7, 46.6, 13.9 ppm. Anal. calcd. for $C_{31}H_{24}BrN_3O_4$ (582.44): C, 63.93; H, 4.15; N, 7.21. Found: C, 63.72; H, 4.17; N, 7.20.

Diethyl-8-(4-fluorophenyl)-9,9-dicyano-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4b)

Yield = 163 mg, 31%. Mp = 261–263 °C. IR (KBr) υ_{max}: 3076, 2983, 2248, 1738, 1699, 1601, 1506, 1446, 1267, 1124, 760 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.12$ (d, $j = 7.6$ Hz, 1H), 8.02 (d, $j = 7.6$ Hz, 1H), 7.60 (dd, J = 8 Hz, 2H), 7.52 (dd, $j = 7.6$ Hz, 1H), 7.39 (dd, $j = 7.6$ Hz, 2H), 7.35 (dd, $j = 8$ Hz, 3H), 7.11 (dd, $j = 7.6$ Hz, Hz, 1H), 6.98 (d, $j = 7.6$ Hz, 1H), 5.87 (s, 1H), 5.10 (s, 1H), 4.38 (q, $j = 7.2$, 1H), 4.21 (q, $j = 7.2$, 1H), 3.96 (q, $j = 7.2$, 2H), 1.22 (t, $j = 7.2$, 3H), 0.97 (t, $j = 7.2$, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.5$, 163.7, 161.5, 154.0, 142.2, 138.0, 131.9, 131.0, 130.4, 129.3, 128.6, 126.1, 124.9, 123.9, 123.5, 122.3, 117.0, 116.3, 116.0,

114.0, 112.1, 79.6, 62.8, 61.9, 61.6, 50.6, 46.8, 13.9, 13.9 ppm. Anal. calcd. for $C_{31}H_{24}FN_3O_4$ (521.54): C, 71.39; H, 4.64; N, 8.06. Found: C, 71.64; H, 4.61; N, 8.05.

Dimethyl-8-(4-bromophenyl)-9,9-dicyano-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4c)

Yield = 194 mg, 35%. Mp = 224–226 °C. IR (KBr) υ_{max}: 3069, 2952, 2364, 1743, 1716, 1597, 1491, 1438, 1269, 1082, 756 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 8.16$ (d, $j = 7.2$ Hz, 1H), 8.03 (d, $j = 7.6$ Hz, 1H), 7.67 (d, $j = 8$ Hz, 2H), 7.60 (dd, $j = 7.6$ Hz, 2H), 7.53 (dd, $j = 7.2$ Hz, 1H), 7.33 (dd, $j = 8$ Hz, 3H), 7.13 (dd, $j = 7.2$ Hz, 1H), 6.97 (d, $j = 7.2$ Hz, 1H), 5.88 (s, 1H), 5.10 (s, 1H), 3.82 (s, 3H), 3.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.9$, 164.4, 143.0, 137.3, 135.1, 132.3, 131.1, 130.7, 130.3, 129.3, 128.7, 126.0, 125.0, 124.1, 123.6, 122.8, 122.6, 122.3, 116.8, 113.9, 112.0, 79.6, 61.9, 53.9, 53.0, 50.6, 47.0 ppm.

Dimethyl-8-(4-chlorophenyl)-9,9-dicyano-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4d)

Yield 167 mg, 33%. Mp = 224–226 °C. IR (KBr) υ_{max}: 3063, 2985, 2273, 1735, 1706, 1600, 1511, 1443, 1263, 1121, 763 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 8.13$ (d, $j = 7.6$ Hz, 1H), 8.01 (d, $j = 8.0$ Hz, 1H), 7.61 (dd, $j = 8.0$ Hz, 2H), 7.54 (d, $j = 8$ Hz, 2H), 7.53 (dd, $j = 7.6$ Hz, 1H), 7.36 (d, $j = 8$ Hz, 2H), 7.33 (dd, $j = 8$ Hz, 1H), 7.13 (dd, $j = 7.6$ Hz, 1H), 6.92 (d, $j = 7.6$ Hz, 1H), 5.88 (s, 1H), 5.12 (s, 1H), 3.82 (s, 3H), 3.57 (s, 3H), ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 165.0$, 164.3, 142.1, 136.5, 134.6, 134.0, 131.1, 130.7, 130.3, 129.4, 128.7, 125.9, 124.9, 124.1, 123.5, 122.8, 122.5, 121.1, 116.8, 114.0, 112.7, 78.4, 61.9, 53.9, 52.9, 50.5, 47.0 ppm. Anal. calcd. for $C_{29}H_{20}ClN_3O_4$ (509.94): C, 68.30; H, 3.95; N, 8.24. Found: C, 68.41; H, 3.97; N, 8.21.

Diethyl-8-(4-chlorophenyl)-9,9-dicyano-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4e)

Yield 177 mg, 33%. Mp = 246–247 °C. IR (KBr) υ_{max}: 3073, 2981, 2366, 1738, 1696, 1591, 1492, 1447, 1268, 1092, 762 cm^{-1}. $\delta = 8.13$ (d, $j = 7.6$ Hz, 1H), 8.01 (d, $j = 8$ Hz, 1H), 7.60 (d, $j = 8.0$ Hz, 2H), 7.54 (d, $j = 8.0$ Hz, 2H), 7.52 (dd, $j = 7.6$ Hz, 1H), 7.36 (d, $j = 8$ Hz, 2H), 7.34 (dd, $j = 7.6$ Hz, 1H), 7.14 (dd, $j = 7.6$ Hz, 1H), 6.92 (d, $j = 7.6$ Hz, 1H), 5.88 (s, 1H), 5.11 (s, 1H), 4.36 (q, $j = 7.2$, 1H), 4.22 (q, $j = 7.2$, 1H), 3.98 (q, $j = 7.2$, 2H), 1.22 (t, $j = 7.2$, 3H), 0.98 (t, $j = 7.2$, 3H), ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.7$, 163.3, 159.2, 151.1, 143.6, 137.7, 131.9, 131.3, 130.6, 129.1, 128.6, 126.5, 125.0, 123.9, 123.6, 122.4, 117.6, 116.9, 116.2, 113.6, 112.1, 77.6, 62.1, 61.9, 61.5, 51.3, 47.2, 13.9, 13.9 ppm.

Dimethyl-9,9-dicyano-8-(2,4-dichlorophenyl)-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4f)

Yield 195 mg, 36%. Mp = 213–214 °C. IR (KBr) $\upsilon_{max} = 3072$, 2987, 2265, 1736, 1702, 1604, 1504, 1439, 1257, 1118, 760 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 8.15$ (d, $j = 6.8$ Hz, 1H), 8.04 (d, $j = 7.6$ Hz, 1H), 7.78 (s, 1H), 7.61 (d, $j = 8$ Hz, 2H), 7.55

(dd, $j = 7.6$ Hz, 2H), 7.36 (d, $j = 6.8$ Hz, 1H), 7.32 (d, $j = 8$ Hz, 1H), 7.19 (dd, $j = 7.6$ Hz, 1H), 7.00 (d, $j = 6.8$ Hz, 1H), 6.01 (s, 1H), 5.71 (s, 1H), 3.82 (s, 3H), 3.59 (s, 3H), ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.7$, 164.4, 143.9, 137.4, 135.5, 134.6, 132.8, 131.1, 130.9, 130.8, 130.3, 130.0, 129.5, 128.7, 128.3, 125.6, 125.1, 124.3, 123.6, 122.8, 122.5, 116.7, 113.4, 112.3, 62.4, 53.9, 53.0, 45.7, 45.6 ppm. Anal. calcd. for $C_{29}H_{19}Cl_2N_3O_4$ (544.38): C, 63.98; H, 3.52; N, 7.72. Found: C, 64.03; H, 3.51; N, 7.19.

Dimethyl-9,9-dicyano-8-(4-nitrophenyl)-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4g)

Yield 177 mg, 34%. Mp = 235–237 °C. IR (KBr) υ_{max}: 3063, 2987, 2356, 1734, 1698, 1590, 1497, 1432, 1267, 1091, 760 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.31$ (d, $J = 8.0$ Hz, 2H), 8.16 (d, $J = 6.8$ Hz, 1H), 8.03 (d, $J = 7.6$ Hz, 1H), 7.81 (t, $J = 7.6$ Hz, 2H), 7.62 (dd, $J = 8.0$ Hz, 2H), 7.55 (d, $J = 6.8$ Hz, 1H), 7.38 (dd, $J = 7.6$, 1H), 7.16 (dd, $J = 7.6$ Hz, 1H), 6.59 (d, $J = 6.8$ Hz, 1H), 5.93 (s, 1H), 5.36 (s, 1H), 3.84 (s, 3H), 3.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.8$, 163.9, 143.2, 137.6, 134.1, 133.5, 131.2, 130.8, 130.1, 129.3, 128.8, 125.0, 124.5, 124.0, 123.3, 122.6, 121.7, 121.5, 116.7, 114.4, 112.0, 76.5, 60.2, 54.2, 52.3, 50.5, 48.1 ppm. Anal. calcd. for $C_{29}H_{20}N_4O_6$ (520.49): C, 66.92; H, 3.87; N, 10.76. Found: C, 66.83; H, 3.89; N, 10.73.

Diethyl-9,9-dicyano-8-(4-nitrophenyl)-9,9a-dihydro-8H-pyrido[1,2-f]phenanthridine-6,7-dicarboxylate (4h)

Yield 180 mg, 33%. Mp = 233–235 °C. IR (KBr) υ_{max}: 3056, 2991, 2347, 1738, 1694, 1593, 1491, 1428, 1271, 1083, 764 cm^{-1}.^{1}H NMR (400 MHz, DMSO): $\delta = 8.31$ (d, $J = 8.0$ Hz, 2H), 8.15 (d, $J = 6.8$ Hz, 1H), 8.03 (d, $J = 7.6$ Hz, 1H), 7.81 (t, $J = 7.6$ Hz, 2H), 7.63 (dd, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 6.8$ Hz, 1H), 7.38 (dd, $J = 7.6$ Hz, 1H), 7.16 (dd, $J = 7.6$ Hz, 1H), 7.00 (d, $J = 6.8$ Hz, 1H), 5.94 (s, 1H), 5.36 (s, 1H), 4.35 (q, $J = 7.2$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 1H), 3.98 (q, $J = 7.2$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): $\delta = 164.4$, 163.7, 143.3, 137.9, 137.7, 131.2, 130.6, 130.3, 130.0, 129.4, 128.8, 125.8, 125.0, 124.4, 124.2, 123.6, 122.3, 122.2, 117.0, 113.6, 111.9, 79.6, 63.0, 61.9, 61.8, 50.4, 46.4, 13.9, 13.9 ppm. Anal. calcd. for $C_{31}H_{24}N_4O_6$ (548.55): C, 67.88; H, 4.41; N, 10.21. Found: C, 67.96; H, 4.42; N, 10.19.

Tetraethyl-9aH-pyrido[1,2-f]phenanthridine-6,7,8,9-tetracarboxylate (7a)

Yield = 258 mg, 50%. Mp = 179–181 °C. IR (KBr) υ_{max}: 2981, 2935, 1742, 1701, 1603, 1486, 1443, 1367, 1235, 1029, 762 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): $\delta = 8.03$ (d, $J = 7.2$ Hz, 1H,), 7.97 (d, $J = 7.6$ Hz, 1H), 7.53 (dd, $J = 7.2$ Hz, 1H), 7.48 (dd, $J = 7.2$ Hz, 2H), 7.44 (dd, $J = 7.2$ Hz, 1H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.05 (d, $J = 7.2$ Hz, 1H), 5.68 (s, 1H), 4.25 (q, $J = 7.6$ Hz, 2H), 4.13 (q, $J = 7.6$ Hz, 2H), 3.96 (q, $J = 7.6$ Hz, 2H), 3.90 (q, $J = 7.6$ Hz, 2H), 1.31 (t, $J = 7.6$ Hz, 3H), 1.12 (t, $J = 7.6$ Hz, 3H), 1.06 (t, $J = 7.6$ Hz, 3H), 0.88 (t, $J = 7.6$ Hz, 3H) ppm. ^{13}C NMR

(100 MHz, DMSO): δ = 166.3, 163.8, 162.8, 161.8, 151.0, 139.6, 137.5, 134.9, 131.4, 130.9, 129.5, 129.3, 129.0, 128.6, 125.4, 124.6, 124.1, 123.1, 110.0, 98.1, 79.6, 62.4, 61.5, 60.9, 56.2, 14.3, 14.1, 14.1, 13.6 ppm. Anal. calcd. for $C_{29}H_{29}NO_8$ (519.54): C, 67.04; H, 5.63; N, 2.70. Found: C, 67.11; H, 5.67; N, 2.69.

Tetramethyl-9aH-pyrido[1,2-*f*]phenanthridine-6,7,8,9-tetracarboxylate (7b)

Yield = 245 mg, 53%. Mp = 273–274 °C. IR (KBr) υ_{max}: 3010, 2954, 1737, 1705, 1604, 1511, 1438, 1358, 1241, 1131 760 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 8.03 (d, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 7.6 Hz), 7.40–7.53 (m, 4H), 7.25 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 7.6 Hz), 5.68 (s, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 165.7, 163.4, 161.1, 160.4, 152.3, 138.4, 136.8, 135.2, 132.9, 130.4, 129.9, 129.1, 128.6, 128.0, 126.7, 125.5, 124.8, 121.3, 107.5, 99.7, 76.6, 56.3, 55.9, 53.6, 52.0 ppm. Anal. calcd. for $C_{25}H_{21}NO_8$ (463.44): C, 64.79; H, 4.57; N, 3.02. Found: C, 64.72; H, 4.57; N, 3.01.

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