Iranian Journal of Organic Chemistry Vol. 16, No. 3(2024) 3861-3866

Green synthesis of pyridoisoquinoline derivatives underUltrasound conditions

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Received: May 2024; Revised: May 2024; Accepted: July 2024

Abstract: An efficient procedure for the synthesis of pyrido[2,1-a]isoquinoline derivatives in excellent yields was investigated using catalyst-free multicomponent reaction of phthaladehyde, methylamine, activated acetylenic compounds, alkyl bromides and triphenylphosphine in water under ultrasonic irradiation at room temperature. In addition, Diels-Alder reactions of pyrido[2,1-a]isoquinoline derivatives with activated acetylenic compounds under ultrasonic irradiation are investigated in two procedures. The advantages of this procedure compared to report methods are short time of reaction, high yields of product, easy separation of product, clean mixture of reaction and green media for performing reaction. In addition, because of having isoquinoline core in synthesized compounds, in this research antioxidant activity of some synthesized compounds was studied.

Keywords: Phthalaldehyde, Four-component reaction, Alkyl bromide, Isoquinoline, Triphenylphosphine, Diels-Alder reactions.

Introduction

In recent years, focus on green chemistry by using environmentally benign reagents and reaction conditions is one of the most fascinating developments in synthesis of widely used organic compounds [1,2]. The use of water as a promising solvent for organic reactions has received considerable attention in the area of organic synthesis owing to its green credentials [3-7], and organic synthesis in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration. Recently a diversity of procedures and mechanisms has been developed based on green chemistry or sonochemistry [8]. Sonochemistry as an original and valuable method has attracted increasing interest in accelerating organic reactions [9-12].This procedure can be very efficient and is applicable to a broad variety of practical synthesis.Luche and coworkers have carried out a number of investigations, which provided the basis for using sonochemistry in organic synthesis [13-16].

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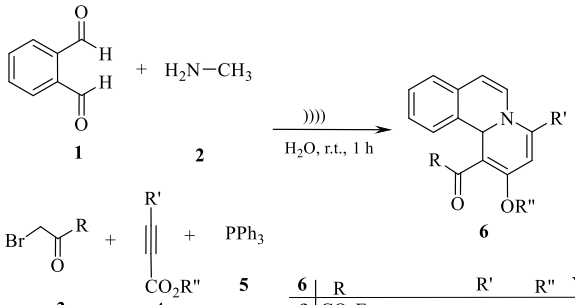
The significantfeatures of the ultrasound approach in organic reactions are improvement of reaction rates, formation of pureproducts with high yields and easier process.This method is also considered as a help in terms of energy protection and waste decreasingwhen compared with traditional methods[17, 18].Ultrasound has increasingly been used in organic synthesis. A large number of ultrasonic reactions can be carried out in higher yield, shorter reaction time or milder conditions. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods [19-22].Also, isoquinolines are an important class of heterocycles and alkaloids that have wide many biologically active as core structures of pharmaceuticals and materials along with applications in synthetic organic chemistry [23-29].Some of natural products have the isoquinoline framework [30, 31]and because of their biological activities and physical properties, they are useful in pharmaceutical compounds and application of them as functional materials [32].Another subject in this research is investigation of antioxidant activity in synthesized compounds. The negative effect of free radicals eliminated by antioxidant activity compounds because of reductive properties and chemical structure of these compounds. These compounds along withit antioxidant activity could be avoid or decrease many illnesses such as Alzheimer, inflammatory bowel syndrome, cardiovascular, cancer and ageing.[33-35] In recent

times, biologists, medicinal and food chemist test and discover new and efficient synthetic antioxidant compounds for protective of humans against these diseases.Herein,In continuation of our attempts to expand new synthetic procedure for chief organic compounds [39-48] we investigated synthesis of pyrido[2,1-a]isoquinoline derivatives in excellent yields (Scheme **1**).

Results and discussion

Chemistry

In this work, generation of pyridoisoquinolinederivatives **6** are performed using phthalaldehyde**1**, methylamine **2**, α-halo substituted carbonyls **3**, activated acetylenic comompouds**4** and triphenylphosphine **5** in water under ultrasonic irradiation condition at room temperature in excellent yield at short time (Scheme **1**).

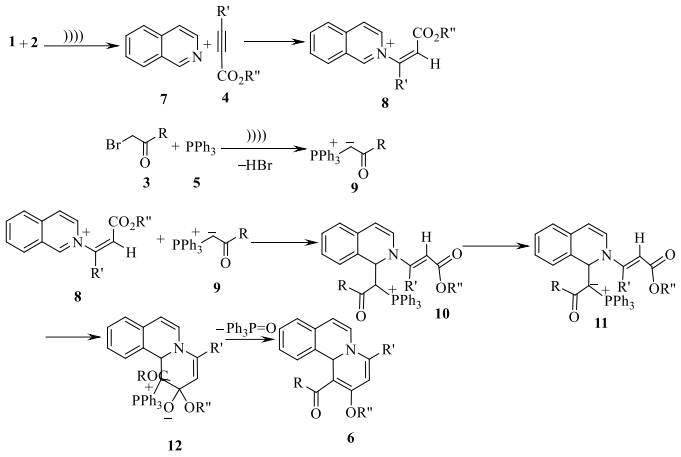


6	R	R'	R"	Yield % of 6
a	CO_2Et	CO_2Me	Me	87
b	CO_2Et	CO_2Et	Et	85
c	CO_2Et	H	Me	85
d	CO_2Et	H	Et	83
e	4-MeO-C_6H_4	CO_2Me	Me	85
f	4-Me-C_6H_4	CO_2Me	Me	89

Scheme 1: Synthesis of pyridoisoquinoline **6**

In the starting stage of this work, catalyst-free reaction of phthalaldehyde**1**, methylamine **2**, ethyl bromopyruvate **3a**, dimethyl acetylenedicarboxylate**4a** and triphenylphosphine **5** in water at room temperature was employed as a sample reaction to achieve the optimum conditions (Table 1). It should been mentioned, these reactions are experimented in both ultrasonic irradiation and conventional conditions and results were exhibited in Table 1. Surprisingly the yield of compound **6a** obtained 87% in short time under ultrasonic irradiation.

The structures of compounds **6** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **6a** exhibited two singlets at 3.86 ppm and 3.98 ppm for methoxy protons, one singlet at 5.32 for –CH proton, one singlet at 6.12 ppm for =CH proton along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to the three carbonyl group of **6a** were observed at δ164.3, 165.6 and 176.6 ppm. The IR spectrum of **6a** was displayed characteristic C=O bands. Although there is no information about the mechanistic details, the reaction can been described by the mechanism proposed in Scheme 2.



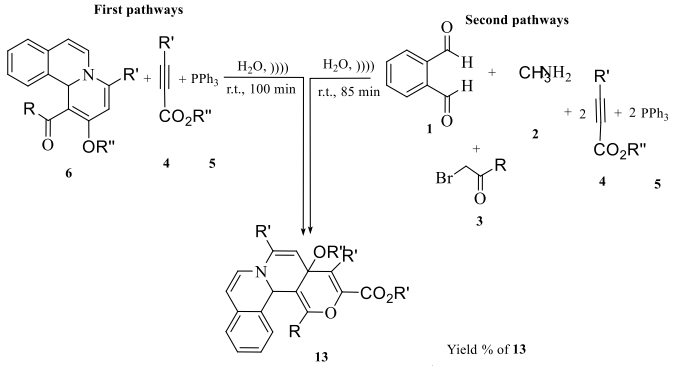
Scheme 2: proposed mechanism for preparation of**6**

First, phthalaldehyde **1** and methylamine **2** reacted under ultrasonic irradiation that is generated isoquinoline **7** that is react with activated acelynic compounds **4** to produce intermediate **8**. In other pot, α-halo substituted carbonyls **3** and triphenylphosphine **5** reacted under similar conditions and produced intermediate **9** by elimination of HBr. Intermediate **9** attacked to intermediate **8** and produced intermediate **10**. Cyclization of intermediate **11** and elimination of triphenylphosphine oxide from intermediate **12** led to produce compound **6**.

Also, the hetero Diels-Alder reaction of pyrido[2,1-a]isoquinoline derivatives **6** with activated acetylenic compounds under ultrasonic irradiation is investigated in two procedures. In first procedure, pyrido[2,1-a]isoquinoline derivatives **6** was separated from mixture of reaction and then reacted with activated acetylenic compounds **4** and triphenylphosphine **5** under ultrasonic irradiation in water and room temperature. In second procedure, compounds **6** without separation performed hetero Diels-Alder reaction under similar conditions (Scheme 3). The results show the yield of reaction in two procedures different completely. As shown in results in Scheme 3, yields of reactions in the second procedure are higher than those in the first procedure that is one of the advantages of multicomponent reactions. In multi step reactions, the yield of final product due to separation of some intermediate is low.

The structures of compounds **13** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. For example, the ^{1}H NMR spectrum of **13a** showed three singlets at 3.56 ppm and 3.78 and 3.83 ppm for methoxy protons, one singlet at 22 for –CH proton, one singlet at 6.28 ppm for =CH proton along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to the three

carbonyl group of **13a** were observed at 161.2, 162.6, 164.5, and 165.7 ppm. The IR spectrum of **13a** was displayed characteristic C=O bands. Although there is no information about the mechanistic details, the reaction can been described by the mechanism proposed in Scheme 4.

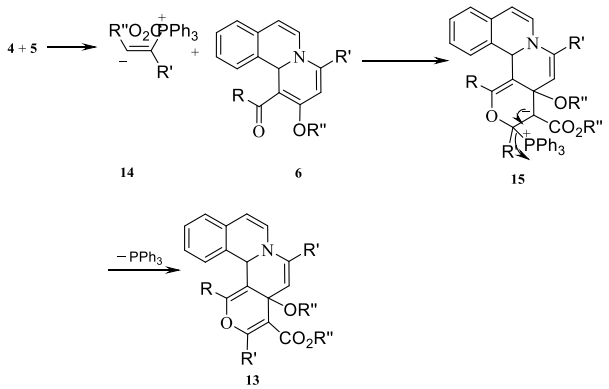


Yield % of **13**

13	R	R'	R"	First procedure	Second procedure
a	CO_2Et	CO_2Me	Me	78	95
b	4-MeO-C_6H_4	CO_2Et	Et	75	92
c	4-Me-C_6H_4	CO_2Me	Me	72	90
d	4-NO_2-C_6H_4	CO_2Me	Me	68	87

Scheme 3. Hetero Diels-Alder reaction for the synthesis of isoquinolines **13**under two procedures

The triphenylphosphine **5** catalyzed hetero Diels–Alder reaction between pyrido[2,1-a]isoquinoline**6** and dialkylacetylenedicarboxylate**4**.[51]Addition of PPh_3**5** to activated acetylene **4** leads to intermediate **14**, which undergoes a Michael-addition reaction and subsequent cyclization with diene moiety of **6** to produce product **13** byelimination of PPh_3.



Scheme 4: Proposed mechanism for preparation of compounds **13**

Conclusion

In summary, multicomponent reaction of phthaladehyde, methylamine, activated acetylenic compounds, alkyl bromides and triphenylphosphine in water under ultrasonic irradiation at room temperature produced pyrido[2,1-a]isoquinoline derivatives in excellent yields. Also, Diels-Alder reaction of pyrido[2,1-a]isoquinoline derivatives with activated acetylenic compounds and triphenylphosphine under ultrasonic irradiation is investigated in two procedures. The chief benefits of our method are high atom economy, green reaction conditions, higher yield, shorter reaction times, and easy work-up, which are in good agreement with some principles of green chemistry.

Experimental

All chemicals used in this work were prepared from Fluka (Buchs, Switzerland) 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. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard**.**

*General procedure for preparation of compounds **6:***

To a stirred mixture of phthalaldehyde**1** (2 mmol) and methylamine **2** (2 mmol) in water (3 mL) under ultrasonic irradiation was added activated acetylenic compounds **4** after 20 min. Alkyl bromide **3** and triphenylphosphine **5** react in another pot in water (3 mL) under ultrasonic irradiation for 15 min. After this time, this mixture added to first pot. After completion the reaction, the solid residue was separated by filtration and washed with Et_2O to afforded pure title compound **6**.

*Methyl 1-(2-ethoxy-2-oxoacetyl)-2-methoxy-11bH-pyrido[2,1-a]isoquinoline-4-carboxylate (**6a**):*

Yellow powder, mp 158-160˚C, Yield: 0.64 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1738, 1725, 1695, 1587, 1489, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.36 (3 H, t, *J* = 7.4 Hz, CH_3), 3.86 (3 H, s, MeO), 3.98 (3 H, s, MeO), 4.35-4.44 (2 H, m, CH_2O), 5.32 (1 H, s, CH), 6.12 (1 H, s, CH), 7.33 (1 H, d, *J* = 7.6 Hz, CH), 7.61-7.81 (3 H, m, 3 CH), 8.77 (1 H, d, *J* = 7.8 Hz, CH), 9.40 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):13.9, 41.2, 52.6, 58.6, 62.7, 101.9, 116.6, 119.1, 123.8, 124.3, 125.7, 127.3, 128.4, 129.4, 130.1, 133.8, 160.6, 164.3, 165.6, 176.6 ppm. MS (EI, 70 eV): *m*/*z* (%) = 369 (M^+, 15), 338 (56), 129 (100), 31 (100). Anal. Calcd for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79. Found: C, 65.18; H, 5.34; N, 3.92 %.

Ethyl 1-(2-ethoxy-2-oxoacetyl)-2-ethoxy-11bH-pyrido[2,1-a]isoquinoline-4-carboxylate (**6b**):

Yellow powder, mp 166-168˚C, Yield: 0.67 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1727, 1692, 1585, 1487, 1286 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.39 (3 H, t, *J* = 7.4 Hz, CH_3), 1.43 (3 H, t, *J* = 7.3 Hz, CH_3), 1.47 (3 H, t, *J* = 7.4 Hz, CH_3), 4.36-4.53 (6 H, m, 3 CH_2O), 5.12 (1 H, s, CH), 6.18 (1 H, s, CH), 7.32 (1 H, d, *J* = 7.6 Hz, CH), 7.62-7.80 (3 H, m, 3 CH), 8.76 (1 H, d, *J* = 7.8 Hz, CH), 9.39 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):13.9 (Me), 14.0 (Me), 14.1, 44.6, 61.9, 62.1, 62.7, 101.6, 116.5, 119.1, 123.7, 124.3, 125.6, 127.3, 128.2, 129.6, 130.1, 133.6 (C), 159.2 (C), 163.9, 165.3, 176.6 ppm. MS (EI, 70 eV): *m*/*z* (%) = 397 (M^+, 15), 352 (68), 129 (100), 45 (100). Anal. Calcd for $C_{22}H_{23}NO_6$ (397.42): C, 66.49; H, 5.83; N, 3.52. Found: C, 66.58; H, 5.96; N, 3.68 %.

Ethyl 2-(2-methoxy-11bH-pyrido[2,1-a]isoquinoline-1-yl)-2-oxoacetate (**6c**):

Pale yellow powder, mp 142-144˚C, Yield: 0.53 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1726, 1697, 1569, 1484, 1287 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.50 (3 H, t, *J* = 7.4 Hz, CH_3), 4.01 (3 H, s, MeO), 4.50 (2 H, q, *J* = 7.4 Hz, CH_2O), 5.24 (1 H, s, CH), 5.63 (1 H, d, *J* = 6.5 Hz, CH), 6.23 (1 H, d, *J* = 6.5 Hz, CH), 7.37 (1 H, d, *J* = 7.6 Hz, CH), 7.72-7.82 (3 H, m, 3 CH), 9.67 (1 H, d, *J* = 7.8 Hz, CH), 9.87 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):14.1, 42.6, 56.7, 62.6, 101.5, 116.6, 120.7, 125.1, 126.9, 128.2, 128.4, 129.5, 130.1, 131.9, 138.4, 160.2, 165.9, 173.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 10), 280 (68), 129 (100), 31 (100). Anal. Calcd for $C_{18}H_{17}NO_4$ (311.33): C, 69.44; H, 5.50; N, 4.50. Found: C, 69.62; H, 5.68; N, 4.67 %.

Ethyl 2-(2-ethoxy-11bH-pyrido[2,1-a]isoquinoline-1-yl)-2-oxoacetate (**6d**):

Pale yellow powder, mp 146-148˚C, Yield: 0.53 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1725, 1695, 1568, 1486, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 0.98 (3 H, t, *J* = 7.4 Hz, CH_3), 1.51 (3 H, t, *J* = 7.4 Hz, CH_3), 4.29 (2 H, q, *J* = 7.4 Hz, CH_2O), 4.47 (2 H, q, *J* = 7.4 Hz, CH_2O), 5.27 (1 H, s, CH), 5.72 (1 H, d, *J* = 6.8 Hz, CH), 6.34 (1 H, d, *J* = 6.8 Hz, CH), 7.38 (1 H, d, ^{3}*J* = 7.5 Hz, CH), 7.73-7.86 (3 H, m, 3 CH), 9.70 (1 H, d, *J* = 7.6 Hz, CH), 9.88 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):14.1, 14.5, 43.4, 60.9, 62.6, 101.8, 116.5, 120.7, 125.1, 126.9, 128.2, 128.5, 130.0, 131.0, 131.8, 138.4, 160.3, 164.3, 173.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 325 (M^+, 15), 280 (48), 129 (100), 45 (100). Anal. Calcd for $C_{19}H_{19}NO_4$ (325.36): C, 70.14; H, 5.89; N, 4.30. Found: C, 70.26; H, 5.98; N, 4.42 %.

Methyl 2-methoxy-1-(4-methoxybenzoyl)-11bH-pyrido[2,1-a]isoquinoline-4-carboxylate (**6e**):

Yellow powder, mp 187-189˚C, Yield: 0.64 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1727, 1695, 1624, 1567, 1458, 1236 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.75 (3 H, s, MeO), 3.83 (3 H, s, MeO), 3.95 (3 H, s, MeO), 5.24 (1 H, s, CH), 6.36 (1 H, s, CH), 7.16 (2 H, d,*J* = 7.6 Hz, 2 CH), 7.35 (1 H, d, *J* = 7.6 Hz, CH), 7.62-7.85 (3 H, m, 3 CH), 8.27 (2 H, *J* = 7.8 Hz, 2 CH), 8.73 (1 H, d, *J* = 7.6 Hz, CH), 9.52 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):48.3, 52.3, 55.6, 58.2, 102.3, 112.4, 116.5, 121.3, 124.2, 125.3, 126.4, 127.5, 128.6, 130.2, 131.2, 131.8, 133.2, 134.3, 158.6, 160.3, 163.4, 189.4 ppm. MS (EI, 70 eV): *m*/*z* (%) = 403 (M^+, 10), 372 (48), 129 (100), 31 (100). Anal. Calcd for $C_{24}H_{21}NO_5$(403.43): C, 71.45; H, 5.25; N, 3.47. Found: C, 71.63; H, 5.43; N, 3.62 %.

Methyl 2-methoxy-1-(4-methylbenzoyl)-11bH-pyrido[2,1-a]isoquinoline-4-carboxylate (**6f**):

Yellow powder, mp 176-178˚C, Yield: 0.64 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1743, 1725, 1697, 1636, 1557, 1484, 1268 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.23 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 5.28 (1 H, s, CH), 6.38 (1 H, s, CH), 7.34 (1 H, d, *J* = 7.6 Hz, CH), 7.48 (2 H, d,*J* = 7.6 Hz, 2 CH), 7.58-7.76 (3 H, m, 3 CH), 7.89 (2 H, d,*J* = 7.6 Hz, 2 CH), 8.68 (1 H, d, *J* = 7.6 Hz, CH), 9.36 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):22.4, 47.6, 55.7, 57.6, 103.4, 117.4, 121.5, 124.4, 125.6, 126.7, 127.3, 127.7, 128.2, 129.2, 130.4, 132.3, 133.4, 135.2, 144.3, 158.7, 163.2, 188.6 ppm. MS (EI, 70 eV): *m*/*z* (%) = 387 (M^+, 10), 356 (62), 129 (100), 31 (100). Anal. Calcd for $C_{24}H_{21}NO_4$ (387.43): C, 74.40; H, 5.46; N, 3.62. Found: C, 74.56; H, 5.62; N, 3.78 %.

*General procedure for preparation of compounds **13***

For the synthesis ofcompounds **13** exists two procedures that are explained in the text. Basis on experiment, second procedure is the best and products have high yield by performing this procedure. To a stirred mixture of phthalaldehyde**1** (2 mmol) and methylamine **2** (2 mmol) in water (3 mL) under ultrasonic irradiation was added activated acetylenic compounds (2 mmol) **4** after 20 min. Alkyl bromide **3** and triphenylphosphine **5** (2 mmol) react in another pot in water (3 mL) under ultrasonic irradiation for 15 min. After this time, this mixture added to first pot. The reaction progress was checked by using thin layer chromatography (TLC). After completion of reaction, activated acetylenic compounds **4** (2 mmol) and triphenylphosphine **5** (2mmol)was added to mixtureunder ultrasonic irradiation. The solid residue separated by filtration and washed with Et_2O to afforded pure title compound **13**.

1-Ethyl 3,4,6,-trimethyl 4a-methoxy-4aH,13bH-pyrano[3,4]pyrido[2,1-a]isoquinoline-1,3,4,6-tetracarboxylate (**13a**):

Pale yellow powder, mp 163-165˚C, Yield: 0.97 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1738, 1697, 1594, 1487, 1283 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.26 (3 H, t, *J* = 7.4 Hz, CH_3), 3.56 (3 H, s, MeO), 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.32-4.45 (2 H, m, CH_2O), 5.22 (1 H, s, CH), 6.28 (1 H, s, CH), 7.26 (1 H, d, *J* = 7.6 Hz, CH), 7.58-7.76 (3 H, m, 3 CH), 8.63 (1 H, d, *J* = 7.8 Hz,

CH), 9.37 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):14.2, 43.6, 51.3, 52.4, 52.8, 53.2, 61.8, 87.2, 108.6, 118.3, 121.2, 124.3, 125.4, 126.3, 127.3, 128.5, 129.4, 134.2, 136.3, 138.3, 142.5, 143.2, 161.2, 162.6, 164.5, 165.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 511 (M^+, 15), 480 (62), 129 (100), 31 (100). Anal. Calcd for $C_{26}H_{25}NO_{10}$ (511.48): C, 61.06; H, 4.93; N, 2.74. Found: C, 61.23; H, 5.18; N, 2.93 %.

Triethyl 4a-ethoxy-1-(4-methoxyphenyl)-4aH,13bH-pyrano[3,4]pyrido[2,1-a]isoquinoline-3,4,6-tetracarboxylate (**13b**):

Yellow powder, mp 181-183˚C, Yield: 1.12 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1745, 1738, 1687, 1634, 1585, 1463, 1242 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (3 H, t, *J* = 7.4 Hz, CH_3), 1.35 (3 H, t, *J* = 7.3 Hz, CH_3), 1.42 (3 H, t, *J* = 7.4 Hz, CH_3), 1.53 (3 H, t, *J* = 7.4 Hz, CH_3), 3.85 (3 H, s, MeO), 3.92-4.12 (2 H, m, CH_2O), 4.23-4.38 (2 H, m, CH_2O), 4.43-4.58 (4 H, m, 2 CH_2O), 5.36 (1 H, s, CH), 6.43 (1 H, s, CH), 7.23 (2 H, d,*J* = 7.6 Hz, 2 CH), 7.38 (1 H, d, *J* = 7.6 Hz, CH), 7.56-7.67 (3 H, m, 3 CH), 7.75 (2 H, *J* = 7.8 Hz, 2 CH), 8.53 (1 H, d, *J* = 7.6 Hz, CH), 9.25 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.5, 13.9, 14.2, 14.5, 49.6, 55.7, 61.2, 61.8, 62.3, 63.4, 81.3, 106.3, 108.5, 112.5, 118.2, 121.7, 124.3, 125.8, 126.2, 126.8, 127.3), 127.9, 128.7, 132.2, 137.6, 141.6, 142.5, 143.7, 160.5, 161.8, 162.4, 163.2 ppm. MS (EI, 70 eV): *m*/*z* (%) = 601 (M^+, 10), 556 (62), 129 (100), 45 (100). Anal. Calcd for $C_{34}H_{35}NO_9$ (601.64): C, 67.87; H, 5.86; N, 2.33. Found: C, 67.98; H, 5.93; N, 2.46 %.

Trimethyl 4a-methoxy-1-(4-methylphenyl)-4aH,13bH-pyrano[3,4]pyrido[2,1-a]isoquinoline-3,4,6-tetracarboxylate (**13c**):

Yellow powder, mp 176-178˚C, Yield: 0.95g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1735, 1696, 1645, 1587, 1468, 1259 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.34 (3 H, s, Me), 3.56 (3 H, s, MeO), 3.75 (3 H, s, MeO), 3.78 (3 H, s, MeO), 3.87 (3 H, s, MeO), 5.27 (1 H, s, CH), 6.34 (1 H, s, CH), 7.32 (2 H, d,*J* = 7.6 Hz, 2 CH), 7.43 (1 H, d, *J* = 7.6 Hz, CH), 7.63-7.72 (3 H, m, 3 CH), 7.78 (2 H, *J* = 7.8 Hz, 2 CH), 8.56 (1 H, d, *J* = 7.6 Hz, CH), 9.32 (1 H, d, *J* = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 22.4, 48.3, 51.3, 52.4, 52.8, 53.4, 81.3, 106.7, 109.3, 118.2, 121.7, 124.6, 124.8, 126.2, 126.7, 127.3, 127.8, 128.2, 128.6, 132.6, 136.8, 138.2, 142.6, 143.9, 145.3, 162.3, 163.2, 164.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 529 (M^+, 10), 498 (68), 129 (100), 31 (100). Anal. Calcd for $C_{30}H_{27}NO_8$ (529.54): C, 68.04; H, 5.14; N, 2.65. Found: C, 68.18; H, 5.26; N, 2.75 %.

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