Supporting Information

THREE-COMPONENT SYNTHESIS OF INDOLIZINES FROM AZAAROMATIC-ACETYLENEDICARBOXYLATE ZWITTERIONS WITH ACYLZIRCONOCENE CHIORIDE COMPLEXES

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General Information

Schwartz reagent [$Cp_2Zr(H)Cl$], anhydrous solvents (CH_2Cl_2 and $ClCH_2CH_2Cl$), isoquinolines **2a**–**d** and pridines **6a**–**c** were obtained from commercial suppliers and used without further purification. All reactions were carried out under an argon atmosphere. For the TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Column chromatography was performed on Silica gel 60N (63-200 μm, Kanto Kagaku Co., Ltd.). ^1H and ^{13}C NMR spectra were measured at 300.4 and 75.5 MHz in $CDCl_3$, and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. Splitting patterns of an apparent multiplet associated with an averaged coupling constant were designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened).

General procedure for the preparation of acylzirconocene chloride 1

CH_2Cl_2 solution of 1: A suspension of Schwartz reagent [$Cp_2Zr(H)Cl$] (258mg, 1.0 mmol) and 1-octene (310 μL, 2.0 mmol) in CH_2Cl_2 (2.5 mL) was stirred at ambient temperature for 30 min and the mixture was treated with carbon monoxide for 2 h (CO balloon, 1 atm). The resulting solution was used in the following experiments without any changes.
$ClCH_2CH_2Cl$ solution of 1: According to the above manner, the solution of **1** in CH_2Cl_2 (2.5 mL) was prepared from $Cp_2Zr(H)Cl$ (258 mg, 1.0 mmol) and1-octene (310 μL, 2.0 mmol). After the CH_2Cl_2 was removed in vacuo, $ClCH_2CH_2Cl$ (2.5 mL) was added to the residue.

General procedure for the synthesis of indolizines 3, 7, and 8c (Scheme 2, 4)

A premixed solution (0 ˚C, 5 min) of azaaromatic compound **2** or **6** (0.5 mmol) and diethyl acetylenedicarboxlate (80 μL, 0.5 mmol) in CH_2Cl_2 or $ClCH_2CH_2Cl$ (2.0 mL) were successively added to a solution of **1** (1.0 mmol) in CH_2Cl_2 or $ClCH_2CH_2Cl$ (2.0 mL) at an ambient temperature. After the consumption of the starting material (by TLC analysis), the reaction mixture was diluted with ether and filtered through a short alumina column. After concentration of the filtrate to dryness, the subsequent purification by silica gel column chromatography (hexane/AcOEt = 20/1) gave the corresponding adduct **3**, **7**, and/or **8c**.

Diethyl 1-octylpyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (3a): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2856, 1724, 1230, 1199. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.88 (t, 3H, *J* = 6.9 *Hz*), 1.26-1.32 (m, 10H), 1.38 (t, 3H, *J* = 7.2 *Hz*), 1.43 (t, 3H, = 7.2 *Hz*), 1.53-1.68 (m, 2H), 3.17 (t, 2H, *J* = 7.9 *Hz*), 4.35 (q, 2H, *J* = 7.2 *Hz*), 4.49 (q, 2H, *J* = 7.2 *Hz*), 6.87 (d, 1H, *J* = 7.6 *Hz*), 7.38-7.59 (m, 3H), 7.63 (d, 1H, *J* = 7.6 *Hz*), 8.28 (dd, 1H, *J* = 8.0, 0.9 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.1, 14.3, 22.6, 24.4, 28.4, 29.2, 29.4, 29.5, 31.8, 60.4, 61.5, 109.4, 113.7, 114.5, 120.6, 123.4, 125.5, 126.6, 127.0, 127.1, 127.6, 128.1, 131.8, 164.7, 168.0. FAB-LM *m/z*: 424 (M^++H^+). FAB-HM Calcd for $C_{26}H_{34}NO_4$: 424.2488; Found: 424.2485. Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H 7.85; N, 3.31; Found: C, 73.56; H, 7.89; N, 3.34.

Diethyl 6-bromo-1-octylpyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (3b): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2854, 1712, 1228, 1191. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.87 (t, 3H, *J* = 6.3 *Hz*), 1.27 (m, 10H), 1.38 (t, 3H, *J* = 7.1 *Hz*), 1.43 (t, 3H, *J* = 7.2 *Hz*), 1.56-1.66 (m, 2H), 3.12 (t, 2H, *J* = 7.5 *Hz*), 4.35 (q, 2H, *J* = 7.1 *Hz*), 4.49 (q, 2H, *J* = 7.2 *Hz*), 7.44-7.53 (m, 2H), 8.22 (d, 1H, *J* = 7.4 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.0, 14.1, 14.2, 22.6, 24.2, 28.4, 29.1, 29.2, 29.4, 31.8, 60.5, 61.6, 109.8, 110.1, 114.7, 121.8, 123.3, 125.4, 125.6, 126.1, 126.9, 12735, 129.0, 131.6, 164.2, 167.6. FAB-LM *m/z*: 501 (M^+). FAB-HM Calcd for $C_{26}H_{32}BrNO_4$: 501.1515, Found: 501.1514. Anal. Calcd for $C_{26}H_{32}BrNO_4$: C, 62.15; H, 6.42; N, 2.79; Found: C, 62.28; H, 6.48; N, 2.91.

Diethyl 7-nitro-1-octylpyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (3c): White solid. MP: 90-91 ºC. IR (KBr) ν cm^{-1}; 2923, 2854, 1712, 1216, 1191. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.87 (t, 3H, *J* = 7.0 *Hz*), 1.26 (m, 10H), 1.38 (t, 3H, *J* = 7.1 *Hz*), 1.43 (t, 3H, *J* = 7.1 *Hz*), 1.58-1.68 (m, 2H), 3.18 (t, 2H, *J* = 7.8 *Hz*), 4.37 (q, 2H, *J* = 7.1 *Hz*), 4.49 (q, 2H, *J* = 7.1 *Hz*), 7.51-7.60 (m, 2H), 7.81 (d, 1H, *J* = 8.1 *Hz*), 8.04 (d, 1H, *J* = 8.0 *Hz*), 8.57 (d, 1H, *J* = 8.3 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.1, 14.3, 22.6, 24.3, 28.5, 29.2, 29.3, 29.5, 31.8, 60.7, 61.8, 107.2, 111.2, 115.8, 120.9, 123.4, 123.9, 124.8, 127.2, 127.3, 128.6, 132.4, 146.3, 164.2, 167.5. FAB-LM *m/z*: 469 (M^++H^+). FAB-HM Calcd for $C_{26}H_{33}N_2O_6$: 469.2339; Found: 469.2333. Anal. Calcd for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 5.98; Found: C, 66.98; H, 6.99; N, 5.86.

Diethyl 8-methyl-1-octylpyrrolo[2,1-a]isoquinoline-2,3-dicarboxylate (3d): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2856, 1708, 1230, 1200. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.87 (t, 3H, *J* = 6.9 *Hz*), 1.24-1.29 (m, 10H), 1.37 (t, 3H, *J* = 7.1 *Hz*), 1.42 (t, 3H, *J* = 7.1 *Hz*), 1.55-1.65 (m, 2H), 2.42 (s, 3H), 3.11 (t, 2H, *J* = 8.0 *Hz*), 4.35 (q, 2H, *J* = 7.1 *Hz*), 4.48 (q, 2H, *J* = 7.1 *Hz*), 6.75 (d, 1H, *J* = 7.5 *Hz*), 7.26-7.30 (m, 2H), 7.55 (d, 1H, *J* = 7.5 *Hz*), 8.21 (d, 1H, *J* = 8.3 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.0, 14.1, 14.2, 21.2, 22.6, 24.3, 28.4, 29.2, 29.3, 29.5, 31.8, 60.3, 61.3, 108.5, 113.5, 114.5, 120.5, 123.1, 123.4, 126.9, 127.0, 127.7, 129.3, 131.3, 136.9, 164.8, 167.9. FAB-LM *m/z*: 438 (M^++H^+). FAB-HM Calcd for $C_{27}H_{36}NO_4$ 438.2644; Found: 438.2641. Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06; N, 3.20; Found: C, 73.91; H, 8.08; N, 3.24.

Diethyl 1-octylpyrrolo[2,1-a]pyridine-2,3-dicarboxylate (7a): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2856, 1724, 1695, 1236, 1213. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.85 (t, 3H, *J* = 7.0 *Hz*), 1.24 (m, 10H), 1.35 (t, 3H, *J* = 7.1 *Hz*), 1.38 (t, 3H, *J* = 7.1 *Hz*), 1.55-1.65 (m, 2H), 2.92 (t, 2H, *J* = 7.5 *Hz*), 4.32 (q, 2H, *J* = 7.1 *Hz*), 4.39 (q, 2H, *J* = 7.1 *Hz*), 6.75 (m, 1H), 7.02 (dd, 1H, *J* = 9.1, 6.8 *Hz*), 7.83 (d, 1H, *J* = 7.1 *Hz*), 8.14 (d, 1H, *J* = 9.1 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.0, 14.2, 14.4, 22.5, 24.2, 27.4, 29.1, 29.2, 29.3, 31.7, 39.7, 61.1, 101.4, 113.1, 120.3, 120.4, 112.2, 122.8, 126.3, 135.0, 163.9, 166.5. FAB-LM *m/z*: 374 (M^++H^+). FAB-HM Calcd for $C_{22}H_{32}NO_4$ 374.2331; Found: 374.2313. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75; Found: C, 70.50; H, 8.29; N, 3.95.

Diethyl 6,8-dimethyl-1-octylpyrrolo[2,1-a]pyridine-2,3-dicarboxylate (7b): White solid. MP: 42-44 ºC. IR (KBr) ν cm^{-1}; 2927, 2856, 1720, 1698, 1240, 1203. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.87 (t, 3H, *J* = 6.9 *Hz*), 1.26 (m, 10H), 1.34 (t, 3H, *J* = 7.1 *Hz*), 1.37 (t, 3H, *J* = 7.1 *Hz*), 1.53-1.63 (m, 2H), 2.21 (s, 3H), 2.39 (s, 3H), 3.11 (t, 2H, *J* = 7.6 *Hz*), 4.32 (q, 2H, *J* = 7.1 *Hz*), 4.36 (q, 2H, *J* = 7.1 *Hz*), 6.45 (s, 1H), 7.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.0, 14.2, 18.4, 19.2, 22.6, 24.5, 27.6, 29.2, 29.3, 29.5, 31.8, 60.3, 61.2, 106.5, 115.1, 117.6, 121.8, 123.6, 128.6, 128.8, 129.2, 165.0, 167.6. FAB-LM *m/z*: 402 (M^++H^+). FAB-HM Calcd for $C_{24}H_{36}NO_4$ 402.2644; Found: 402.2648. Anal. Calcd for $C_{24}H_{35}NO_4$: C, 71.79; H, 8.79; N, 3.49; Found: C, 71.65; H, 8.58; N, 3.36.

2,3-Diethyl 8-methyl 1-octylpyrrolo[2,1-a]pyridine-2,3,8-tricarboxylate (7c): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2856, 1731, 1716, 1276, 1199. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.86 (t, 3H, *J* = 6.9 *Hz*), 1.25 (m, 10H), 1.36 (t, 3H, *J* = 7.1 *Hz*), 1.37 (t, 3H, *J* = 7.2 *Hz*), 3.13 (t, 2H, *J* = 7.9 *Hz*), 3.88 (s, 3H), 4.33 (q, 2H, *J* = 7.1 *Hz*), 4.34 (q, 2H, *J* = 7.2 *Hz*), 6.70 (t, 1H, *J* = 7.0 *Hz*), 7.42 (d, 1H, *J* = 7.0 *Hz*), 7.92 (d, 1H, *J* = 7.0 *Hz*). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.0, 14.2, 22.6, 24.4, 27.7, 29.2, 29.3, 29.5, 31.8, 52.2, 60.7, 60.8, 107.8, 111.2, 117.5, 123.9, 124.4, 125.6, 126.5, 129.3, 164.7, 165.9, 166.0. FAB-LM *m/z*: 432 (M^++H^+). FAB-HM Calcd for $C_{24}H_{34}NO_6$ 432.2386; Found: 432.2390. Anal. Calcd for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N, 3.25; Found: C, 66.85; H, 7.56; N, 3.25.

2,3-Diethyl 6-methyl 1-octylpyrrolo[2,1-a]pyridine-2,3,6-tricarboxylate (8c): Colorless oil. IR (neat) ν cm^{-1}; 2927, 2856, 1727, 1701, 1236, 1213. ^{1}H NMR (300 MHz, $CDCl_3$) δ; 0.86 (t, 3H, *J* = 7.0 *Hz*), 1.25 (m, 10H), 1.37 (t, 3H, *J* = 7.1 *Hz*), 1.39 (t, 3H, *J* = 7.1 *Hz*), 1.59-1.69 (m, 2H), 3.00 (t, 2H, *J* = 7.7 *Hz*), 3.96 (s, 3H), 4.35 (q, 2H, *J* = 7.1 *Hz*), 4.41 (q, 2H, *J* = 7.1 *Hz*), 7.55 (d, 1H, *J* = 9.5 *Hz*), 8.15 (d, 1H, *J* = 9.5 *Hz*), 8.63 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ; 14.1, 14.2, 14.4, 22.6, 24.2, 27.7, 29.1, 29.2, 29.3, 29.7, 31.8, 52.5, 60.1, 61.4, 103.1, 117.0, 119.8, 121.2, 122.1, 127.4, 127.8, 135.1, 163.6, 165.5, 166.0.

FAB-LM *m/z*: 432 (M^++H^+). FAB-HM Calcd for $C_{24}H_{34}NO_6$ 432.2386; Found: 432.2391. Anal. Calcd for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N, 3.25; Found: 67.03; H, 8.01; N, 3.23.

Two-step synthesis of indolizine 3a from 2a and DEAD with α-nitroketone 4 (Scheme 3)

To a solution of 1-nitrononan-2-one (**4**, 94 mg, 0.5 mmol) and diethyl acetylenedicarboxlate (80 μL, 0.5 mmol) in 1 mL H_2O–MeCN (5:1) was added isoquinoline (**2a**, 59 μL, 0.5 mmol) at an ambient temperature. After being stirred at the same temperature for 24 h, the reaction mixture was quenched by the addition of 1 M HCl and extracted with ether. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The residue (44.8 mg) was dissolved in 1.3 mL CH_2Cl_2–trifluoroacetic acid (10:3), and then treated with Et_3SiH (160 μl, 1.0 mmol) at an ambient temperature for 58 h.The reaction mixture was quenched by the addition of sat. $NaHCO_3$ and extracted with ether. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The subsequent purification by silica gel column chromatography (hexane/AcOEt = 20/1) gave the corresponding adduct **3a** (37.9 mg, 18%).