Electronic Supplementary Material (ESI) for RSC Advances.

Tuneable radical cyclisations: A tin free approach towards tricyclic and spirocyclic heterocycles *via* a common precursor

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Electronic Supplementary Information

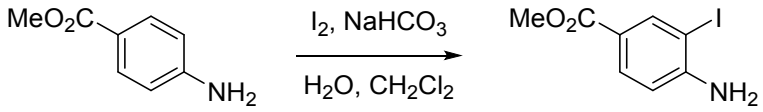
Contents

Experimental procedures and analytical data

General experimental

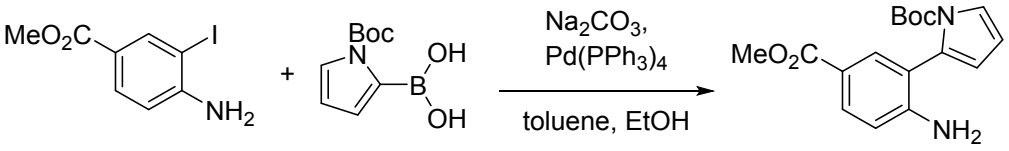
All reactions were carried out under an atmosphere of nitrogen and all glassware was pre-dried in an oven (110 ^{o}C) and cooled under nitrogen prior to use. Stirring was by internal magnetic follower unless otherwise stated. Analytical TLC was carried out on Merck 60 F_{245} aluminium-backed silica gel plates. Short wave UV (245 nm), iodine, $KMnO_4$ or vanillin were used to visualise components.
Tetrahydrofuran, dichloromethane and toluene were purchased as anhydrous solvents from Sigma-Aldrich. All other reagents and solvents were purchased were used as received from commercial sources.
^{1}H and ^{13}C NMR data were recorded on a Bruker AV400 or a Bruker AV500 spectrometer. Spectra were recorded in deuterochloroform and referenced to residual $CHCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hz. The following abbreviations are used to describe multiplicity; s-singlet, d-doublet, t-triplet, q-quartet and m-multiplet. High resolution mass spectra were recorded on an Agilent QTOF LC/MS 6520 utilising electrospray ionisation (recorded in the positive mode) with a methanol mobile phase. Melting points were determined using open glass capillaries on a Stuart Scientific SMP3 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1605 FT-IR spectrophotometer using NaCl plates or on a Bruker Alpha IR spectrophotometer.

Methyl 4-amino-3-iodobenzoate (13)[1]



Sodium bicarbonate (2.83 g, 33.7 mmol) and iodine (7.56 g, 29.8 mmol) were added sequentially to a stirred biphasic solution of methyl 4-aminobenzoate (3.00 g, 19.9 mmol) in CH_2Cl_2 (35 mL) and water (30 mL). The resulting mixture was stirred overnight at room temperature, after which a further portion of iodine (1.50 g, 5.92 mmol) was added and the resulting dark mixture stirred for a further 24 hours. Solid sodium thiosulfate was added and the organic phase separated. The organic phase was washed with water (2 × 30 mL), brine (2 × 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified *via* Biotage (3:1 pet ether/EtOAc; snap 25 g column) to give methyl 4-amino-3-iodobenzoate (**13**) (4.40 g, 80%) as a pale yellow solid; m.p. 91-93 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3470 (NH_2), 3362 (NH_2), 3202 (CH), 2947 (CH), 1682 (C=O); δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 2.0, Ar*H*), 7.80 (1H, dd, *J* 8.5, 2.0, Ar*H*), 6.69 (1H, d, *J* 8.5, Ar*H*), 4.54 (2H, br. s, NH_2), 3.85 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 165.7 (C), 150.7 (C), 141.0 (CH), 131.1 (CH), 121.2 (C), 113.1 (CH), 82.1 (C), 51.8 (CH_3); *m/z* (ES) 277.9690 ([M+H]$^+$, $C_8H_9INO_2$ requires 277.9678).

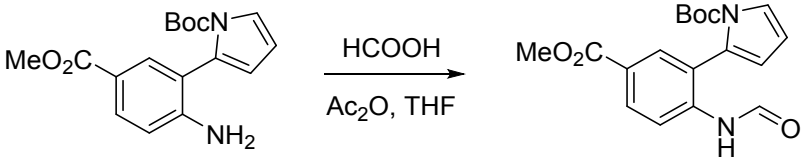
***tert*-Butyl 2-(2-amino-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (15)**



$Pd(Ph_3P)_4$ (0.31 g, 0.27 mmol) and aqueous sodium carbonate (28.0 mL of a 2 M solution 56.0 mmol) were added to a solution of methyl 4-amino-3-iodobenzoate (**13**) (1.50 g, 5.41 mmol) and (1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-yl)boronic acid (1.14 g, 5.41 mmol) in toluene (54.2 mL) and ethanol (27.1 mL). The mixture was heated at 80 °C for 18 hours and allowed to cool to room temperature. EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (25 mL) were added and the layers separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified *via* Biotage (4:1 pet ether/EtOAc; snap 45 g column) to give *tert*-butyl 2-(2-amino-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (**15**) (1.41 g, 82%) as a yellow solid; m.p. 128-130 ^{o}C; ν_{max} (CH_2Cl_2)/cm^{-1} 3425 (NH_2), 1639 (C=O), 1623 (C=O); δ_H (400 MHz, $CDCl_3$) 7.82 (1H, dd, *J*

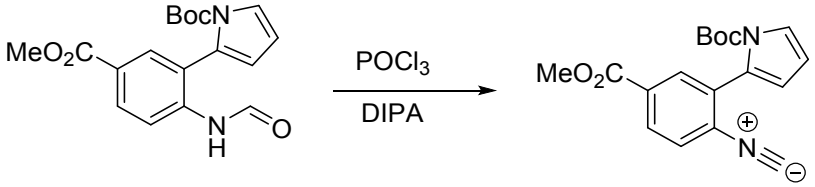
8.3, 2.0, Ar*H*), 7.77 (1H, d, *J* 2.0, Ar*H*), 7.41 (1H, dd, *J* 3.3, 1.5, Ar*H*), 6.65 (1H, d, *J* 8.6, Ar*H*), 6.26 (1H, t, *J* 3.3, Ar*H*), 6.20 (1H, dd, *J* 3.3, 1.8, Ar*H*), 4.09 (2H, s, NH_2), 3.83 (3H, s, CH_3), 1.27 (9H, s, (CH_3)$_3$); δ_C (101 MHz, $CDCl_3$) 167.1 (C), 150.0 (C), 149.1 (C), 133.0 (CH), 130.9 (CH), 129.4 (C), 122.4 (CH), 119.6 (C), 118.8 (C), 114.8 (CH), 113.6 (CH), 110.8 (CH), 83.6 (C), 51.5 (CH_3), 27.3 (CH_3); *m/z* (ES) 317.1508 ([M+H]$^+$, $C_{17}H_{21}N_2O_4$ requires 317.1501).

***tert*-Butyl 2-(2-formamido-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (16)**



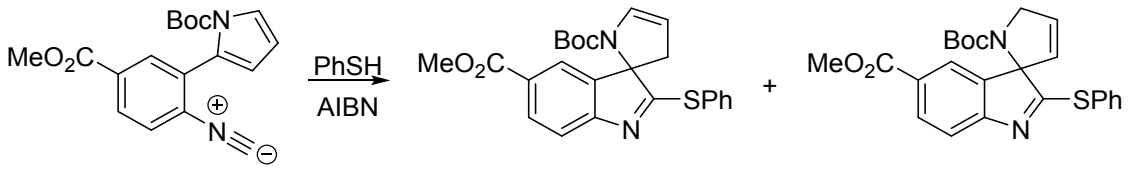
Formic acid (0.02 mL, 0.41 mmol) was added to a stirred solution of acetic anhydride (0.04 mL, 0.41 mmol) in THF (5 mL) at 0 °C. The resulting mixture was heated to reflux for 2 hours. The reaction mixture was the re-cooled to 0 °C and a solution of *tert*-butyl 2-(2-amino-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (0.13 g, 0.41 mmol) in THF (5 mL) was added and then stirred at room temperature for 5 hours. A saturated aqueous solution of Na_2CO_3 (10 mL) was added and solvent removed under reduced pressure. The aqueous phase was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified *via* Biotage (3:1 pet ether/EtOAc, snap 25 g column) to give a mixture of amide rotamers (7:3) *tert*-butyl 2-(2-formamido-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (**16**) (0.13 g, 95%) as a colourless solid; m.p. 128-130 ^oC; ν_{max} (CH_2Cl_2)/cm^{-1} 3385 (NH), 1740 (C=O), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 8.74 (0.3H, d, *J* 11.1, C*H*O), 8.48 (0.7H, d, *J* 8.6, C*H*O), 8.35 (0.7H, s, Ar*H*), 8.04 (1H, dd, *J* 8.6, 1.6, Ar*H*), 7.95 (0.3H, s, Ar*H*), 7.90 (0.7H, d, *J* 1.5, Ar*H*), 7.60 (0.7H, br. s, N*H*), 7.57 (0.3H, br. s, N*H*), 7.46 (0.7H, dd, *J* 3.4, 1.9, Ar*H*), 7.42 (0.3H, s, Ar*H*), 7.32 (0.3H, d, *J* 8.6, Ar*H*), 6.29 (1H, dd, *J* 3.3, 3.3, Ar*H*), 6.23 - 6.27 (1H, m, Ar*H*), 3.89 (3H, s, CH_3), 1.22 (9H, s, (CH_3)$_3$); δ_C (101 MHz, $CDCl_3$) 166.2 (C), 166.0 (C), 161.3 (CH), 159.0 (CH), 148.6 (C), 148.4 (C), 140.1 (C), 140.0 (2 × C), 133.3 (CH), 132.3 (CH), 130.7 (CH), 130.5 (CH), 127.1 (2 × C), 125.9 (C), 125.3 (C), 125.0 (C), 124.3 (C), 123.2 (2 × CH), 119.8 (CH), 116.2 (CH), 116.1 (2 × CH), 111.1 (CH), 111.0 (CH), 84.4 (C), 84.2 (C), 52.1 (CH_3), 52.0 (CH_3), 27.5 (CH_3), 27.3 (CH_3); *m/z* (ES) 345.1441 ([M+H]$^+$, $C_{18}H_{21}N_2O_5$ requires 345.1451).

***tert*-Butyl 2-(5-(methoxycarbonyl)-2-(methyleneamino)phenyl)-1*H*-pyrrole-1-carboxylate (11)**



Diisopropylamine (1.26 mL, 8.97 mmol) was added to a solution of *tert*-butyl 2-(2-formamido-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (**16**) (0.52 g, 1.49 mmol) in CH_2Cl_2 (20 mL) at 0 °C followed by dropwise addition of phosphorus oxychloride (0.29 mL, 3.13 mmol). The solution was stirred for 30 min at 0 °C and then at room temperature for 2 hours. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (20 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (30 mL), brine (30mL), dried over $MgSO_4$ and solvent concentrated under reduced pressure. The residue was purified *via* Biotage (6:1 pet ether/EtOAc, snap 25 g column) to give *tert*-butyl 2-(5-(methoxycarbonyl)-2-(methyleneamino)phenyl)-1*H*-pyrrole-1-carboxylate (**11**) (0.38 g, 79%) as a colourless solid; mp 115-116 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 2981 (CH), 2121 (N=C), 1746 (C=O), 1727 (C=O), 1248 (C-O), 1149 (C-O); δ_H (400 MHz, $CDCl_3$) 8.05-8.07 (1H, m, Ar*H*), 8.02 (1H, dd, *J* 8.2, 1.9, Ar*H*), 7.43-7.48 (2H, m, Ar*H*), 6.30 (1H, s, Ar*H*), 6.29 (1H, d, *J* 1.0, Ar*H*), 3.93 (3H, s, CH_3), 1.40 (9H, s, (CH_3)$_3$); δ_C (101 MHz, $CDCl_3$) 168.9 (**C**), 165.4 (**C**), 148.6 (**C**), 132.9 (**C**), 131.9 (**C**H), 130.4 (**C**), 129.8 (C), 129.5 (**C**H), 127.9 (**C**), 126.6 (**C**H), 123.3 (**C**H), 116.2 (**C**H), 110.9 (**C**H), 84.2 (**C**), 52.5 (**C**H$_3$), 27.6 (3 × **C**H$_3$); *m/z* 349.1152 ([M+Na]$^+$, $C_{18}H_{19}N_2O_4$ requires 349.1164).

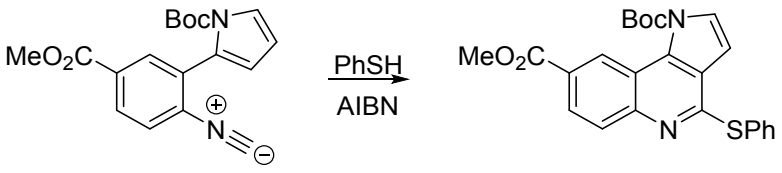
1'-(*tert*-Butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(5'H)-dicarboxylate (17) and 1'-(*tert*-butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(3'H)-dicarboxylate (9)



To a solution of *tert*-butyl 2-(5-(methoxycarbonyl)-2-(methyleneamino)phenyl)-1*H*-pyrrole-1-carboxylate (**11**) (0.05 g, 0.15 mmol) in toluene (5.08 mL) under a N_2 atmosphere was added thiophenol (0.08 mL, 0.76 mmol) followed by 2,2'-(diazene-1,2-diyl)bis(2-

methylpropanenitrile) (7.50 mg, 0.05 mmol). The resulting solution was stirred for 2 hours at 80 °C. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified via Biotage (4:1 Petol/EtOAc; zip 30 g column) to give 1'-(*tert*-butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(5'H)-dicarboxylate (**17**) (0.012 g, 18%) as a colourless oil followed by 1'-(*tert*-butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(3'H)-dicarboxylate (**9**) (0.03 g, 47%) as a colourless oil; (**17**) ν_{max} (neat) 2928 (C-H), 1713 (C=O); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* 8.1, 1.8, Ar*H*), 7.98 (1H, d, *J* 1.8, Ar*H*), 7.65-7.70 (2H, m, 2 × Ar*H*), 7.45-7.48 (3H, m, 3 × Ar*H*), 7.35 (1H, d, *J* 8.1, Ar*H*), 6.87 (1H, ddd, *J* 4.3, 2.3, 2.3, Ar*H*), 5.18 (1H, ddd, *J* 4.3, 2.3, 2.3, Ar*H*), 3.91 (3H, s, OC***H*₃**), 3.27 (1H, ddd, *J* 17.1, 2.3, 2.3, 1 × CH_2), 3.02 (1H, ddd, *J* 17.1, 2.3, 2.3, 1 × CH_2), 1.07 (9H, s, 3 × C***H*₃**); δ_C (126 MHz, $CDCl_3$) 187.0 (C), 166.9 (C), 157.6 (C), 150.7 (C), 142.9 (C), 134.5 (2 × CH), 131.4 (CH), 130.8 (CH), 129.6 (CH), 129.4 (2 × CH), 126.9 (C), 126.7 (C), 121.9 (CH), 119.0 (CH), 104.7 (CH), 81.6 (C), 76.4 (C), 52.1 (CH_3), 43.7 (CH_2), 27.7 (3 × CH_3); *m/z* (APCI) 437.1525 ([M + H]$^+$, $C_{24}H_{25}N_2O_4S$ requires 437.1530). (**9**) ν_{max} (neat) 2976 (C-H), 1706 (C=O), 1614 (C=O); δ_H (400 MHz, $CDCl_3$) 8.02 (1H, dd, *J* 8.2, 1.9, Ar*H*), 7.80 (1H, d, *J* 2.0, Ar*H*), 7.63-7.68 (2H, m, 2 × Ar*H*), 7.47-7.43 (3H, m, 3 × Ar*H*), 7.35 (1H, d, *J* 8.1, Ar*H*), 6.26 (1H, ddd, *J* 6.3, 2.0, 2.0, Ar*H*), 5.37 (1H, ddd, *J* 6.3, 2.0, 2.0, Ar*H*), 4.56 (1H, ddd, *J* 15.9, 2.0, 2.0, 1 × CH_2), 4.42 (1H, ddd, *J* 15.9, 2.0, 2.0, 1 × CH_2), 3.89 (3H, s, OC***H*₃**), 1.08 (9H, s, 3 × C***H*₃**); δ_C (101 MHz, $CDCl_3$) 186.5 (C), 166.9 (C), 158.0 (C), 152.3 (C), 140.2 (C), 134.3 (2 × CH), 131.6 (CH), 129.8 (CH), 129.5 (CH), 129.3 (2 × CH), 128.9 (CH), 127.3 (C), 126.5 (C), 122.9 (CH), 119.0 (CH), 83.4 (C), 80.9 (C), 54.3 (CH_2), 52.1 (CH_3), 27.8 (3 × CH_3); *m/z* (NSI) 437.1532 ([M + H]$^+$, $C_{24}H_{25}N_2O_4S$ requires 437.1530).

1-*tert*-butyl 8-methyl 4-(phenylthio)-1*H*-pyrrolo[3,2-c]quinoline-1,8(3aH,9bH)-dicarboxylate (8)



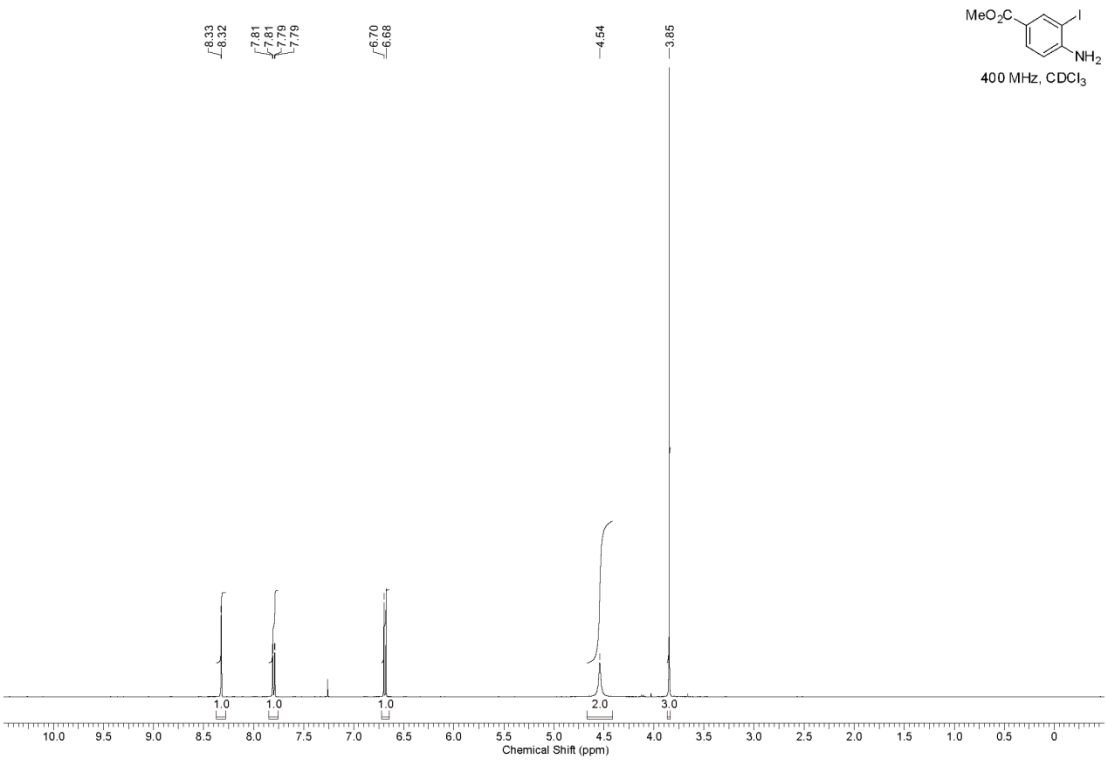
To a solution of *tert*-butyl 2-(5-(methoxycarbonyl)-2-(methyleneamino)phenyl)-1*H*-pyrrole-1-carboxylate (0.05 g, 0.15 mmol) in toluene (3.06 ml) under a N_2 atmosphere was added benzenethiol (0.08 ml, 0.77 mmol) followed by 2,2'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (2.52 mg, 0.015 mmol). The resulting solution was stirred for 2 hours at 80 °C. The mixture was cooled to room temperature and concentrated under reduced

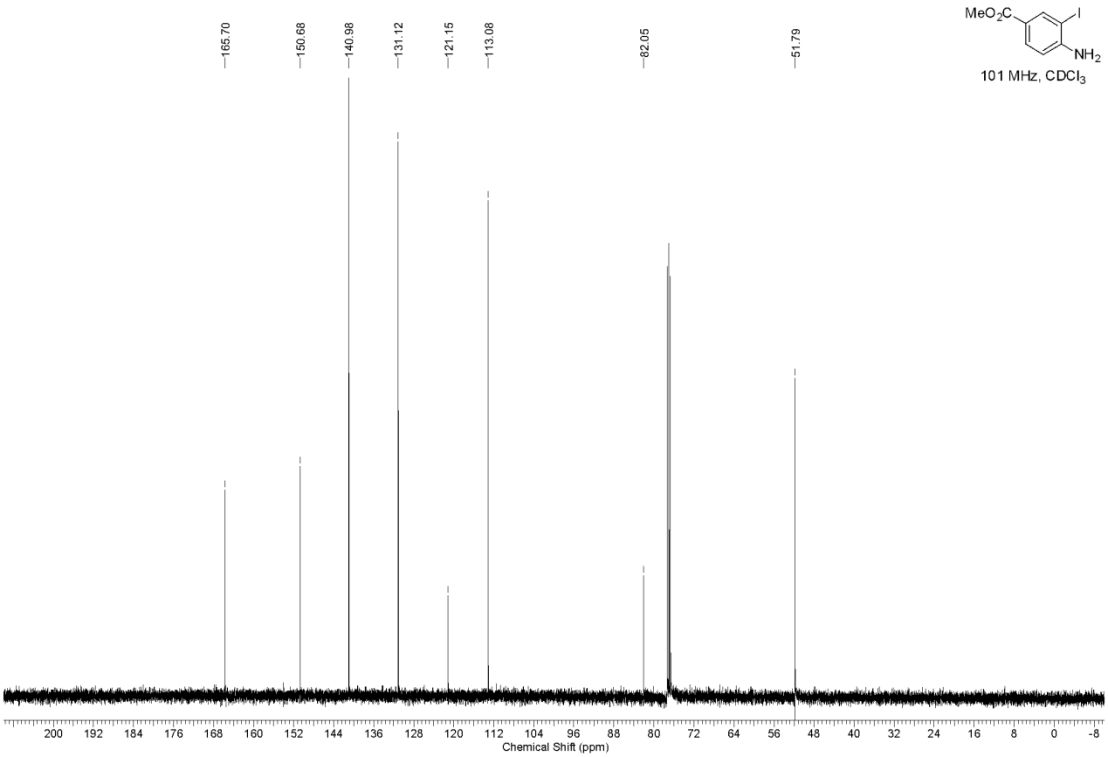
pressure. The residue was purified via Biotage (8:2 pet/EtOAc; snap 10 g column) to give 1'-(*tert*-butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(5'H)-dicarboxylate (**9**) (0.004 g, 5%) as a colorless oil followed by 1-*tert*-butyl 8-methyl 4-(phenylthio)-1*H*-pyrrolo[3,2-c]quinoline-1,8(3aH,9bH)-dicarboxylate (**8**) (0.04 g, 62%) as a colourless oil; ν_{max} (CH_2Cl_2) cm^{-1} 3060 (C-H), 2950 (C-H), 1739 (C=O), 1706 (C=O); δ_H (400 MHz, $CDCl_3$) 8.12 (1H, dd, *J* 8.3, 1.8, Ar*H*), 7.76 (1H, d, *J* 1.8, Ar*H*), 7.60-7.64 (2H, m, 2 × Ar*H*), 7.43-7.48 (4H, m, Ar*H*), 6.70 (1H, d, *J* 5.8, Ar*H*), 6.41 (1H, d, *J* 5.8, Ar*H*), 3.92 (3H, s, CH_3), 1.22 (9H, s, (CH_3)$_3$); δ_C (101 MHz, $CDCl_3$) 181.0 (C), 168.6 (C), 166.3 (C), 158.3 (2 × C), 146.9 (C), 146.4 (CH), 134.5 (2 × CH), 134.4 (C), 132.6 (CH), 130.1 (CH), 129.6 (2 × CH), 127.4 (C), 127.3 (CH), 126.0 (C), 122.6 (CH), 119.8 (CH), 84.3 (C), 52.2 (CH_3), 27.8 (3 × CH_3); *m/z* (ES) 473.0958 ($[M + K]^+$, $C_{24}H_{22}N_2O_4SK$ requires 473.0938).

References

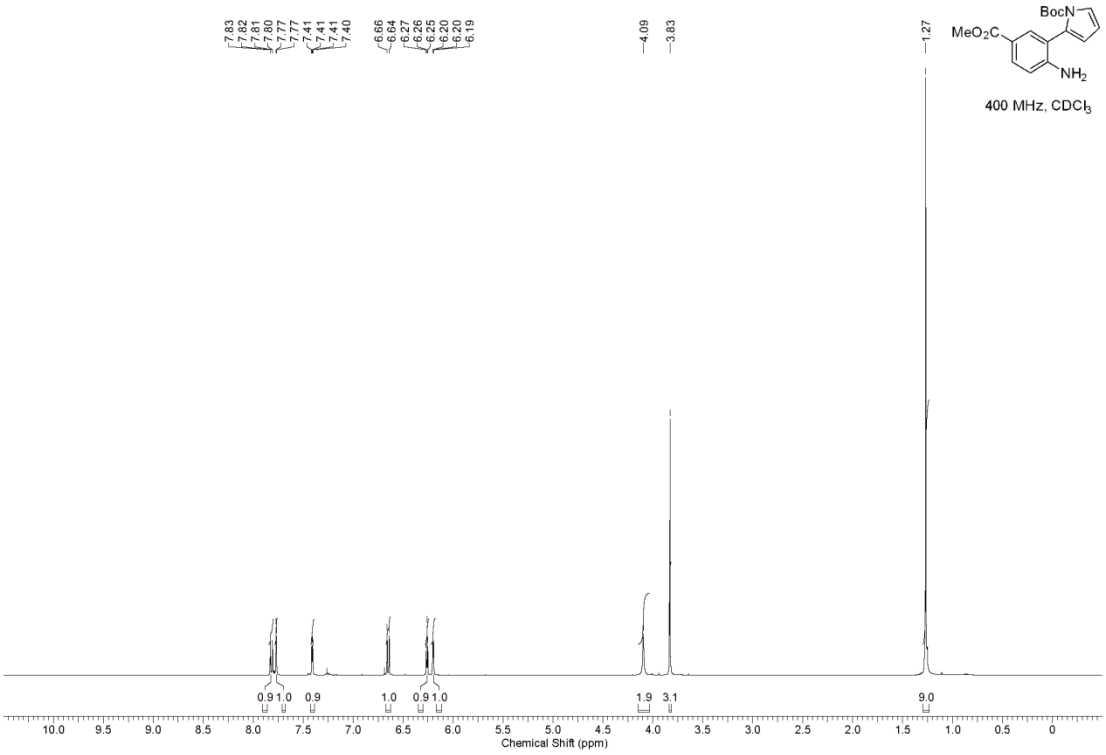
1) A. G. Arvanitis, P. J. Gilligan *et al*., *J. Med. Chem.*, 1999, **42**, 805.

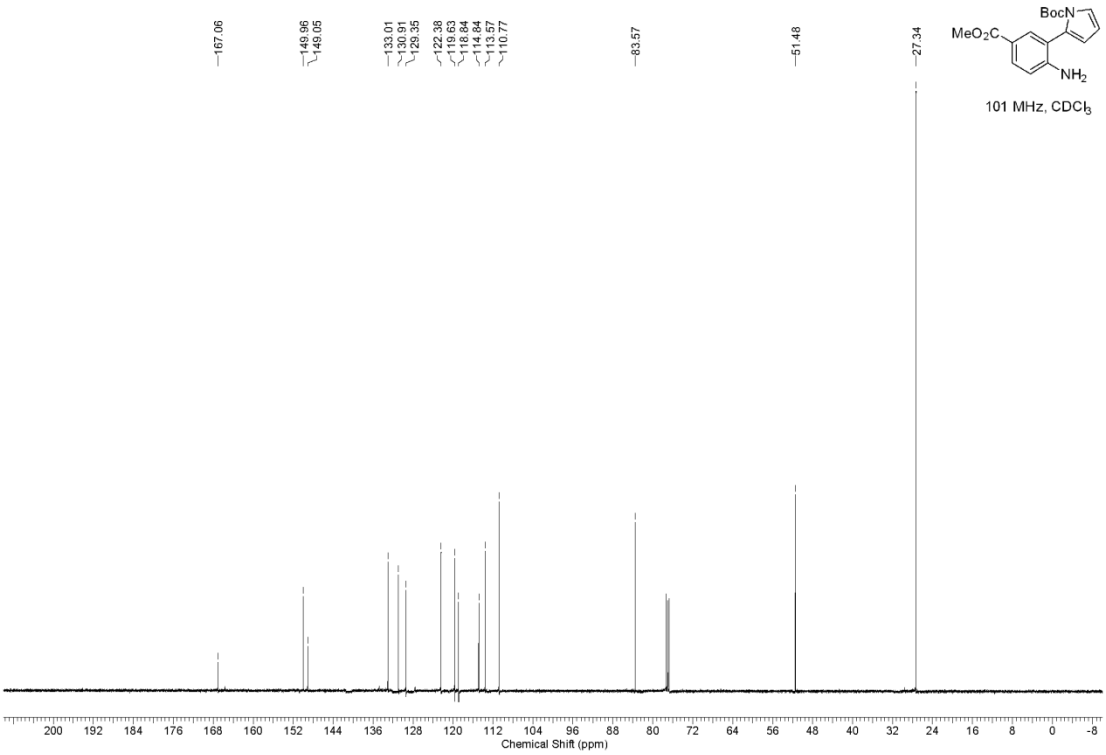
Methyl 4-amino-3-iodobenzoate (13)





tert-Butyl 2-(2-amino-5-(methoxycarbonyl)phenyl)-1*H*-pyrrole-1-carboxylate (15)





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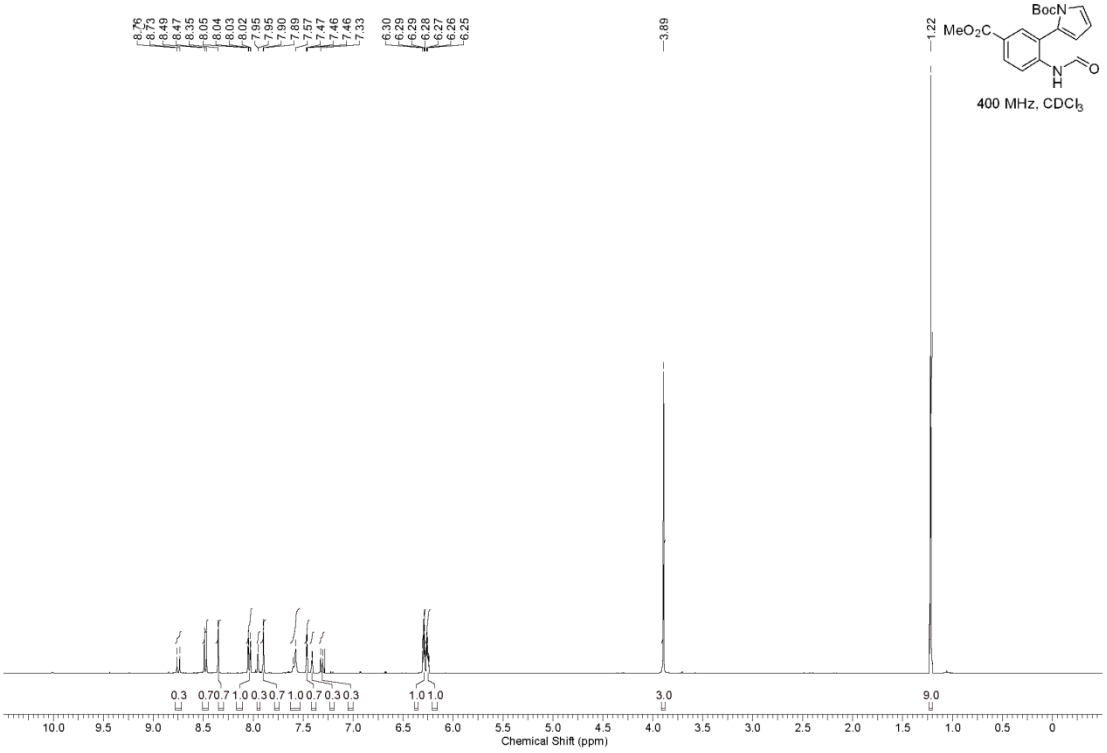
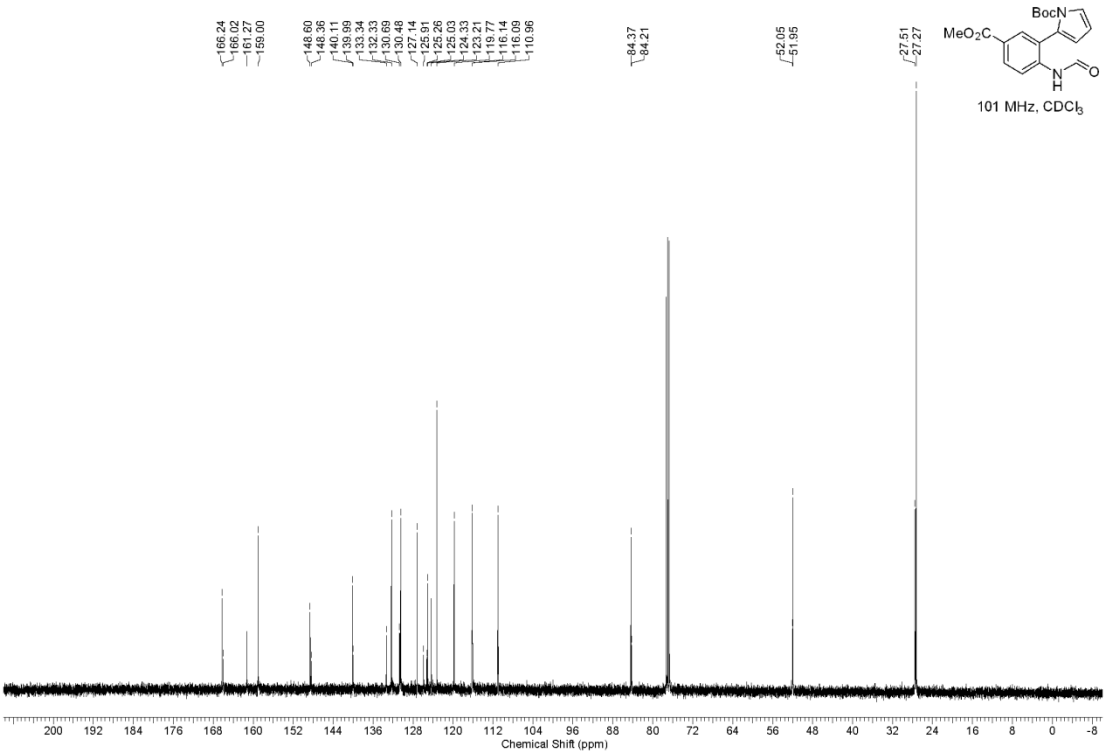
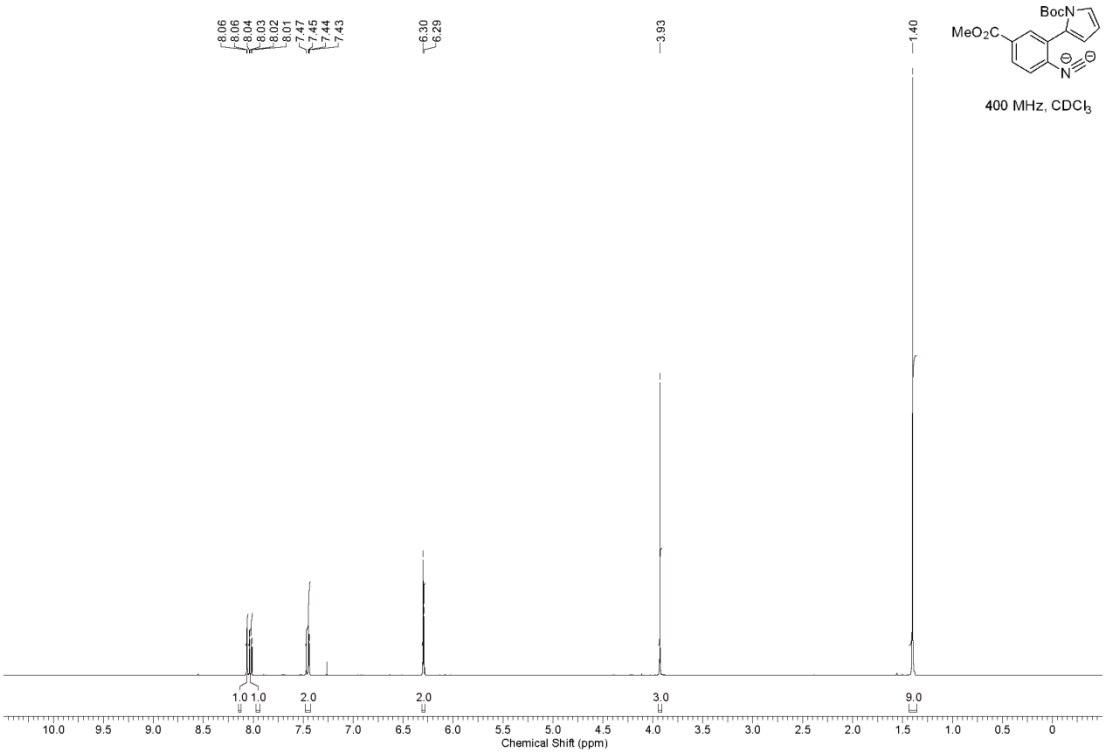
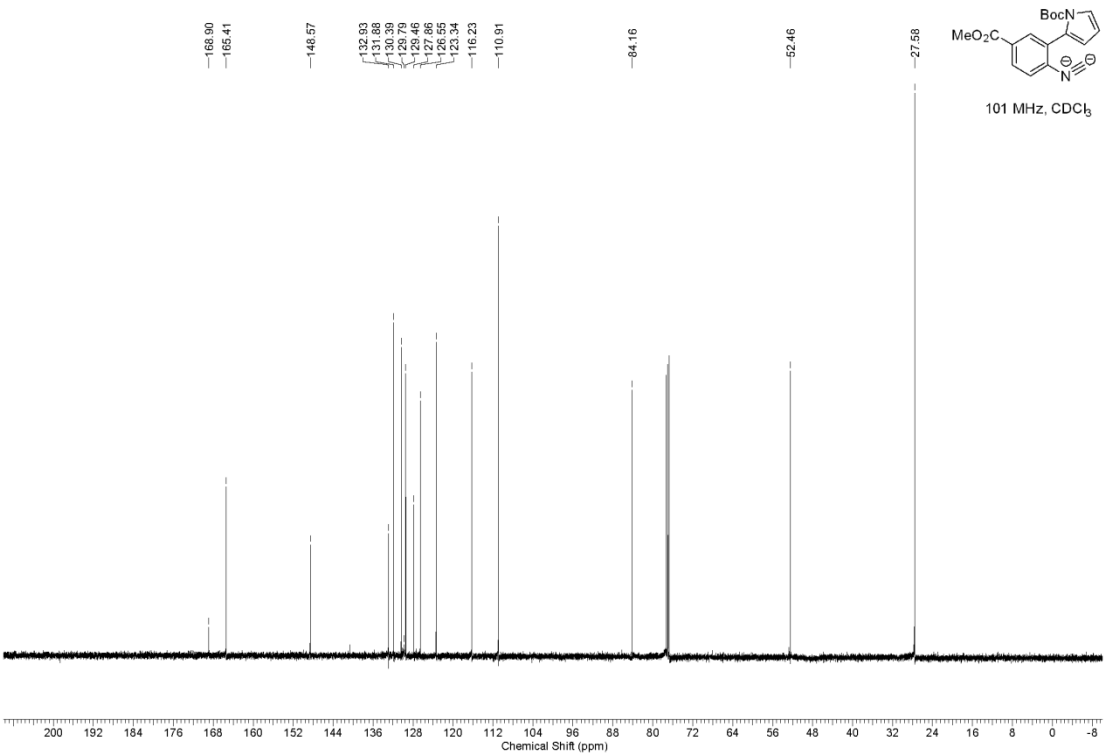


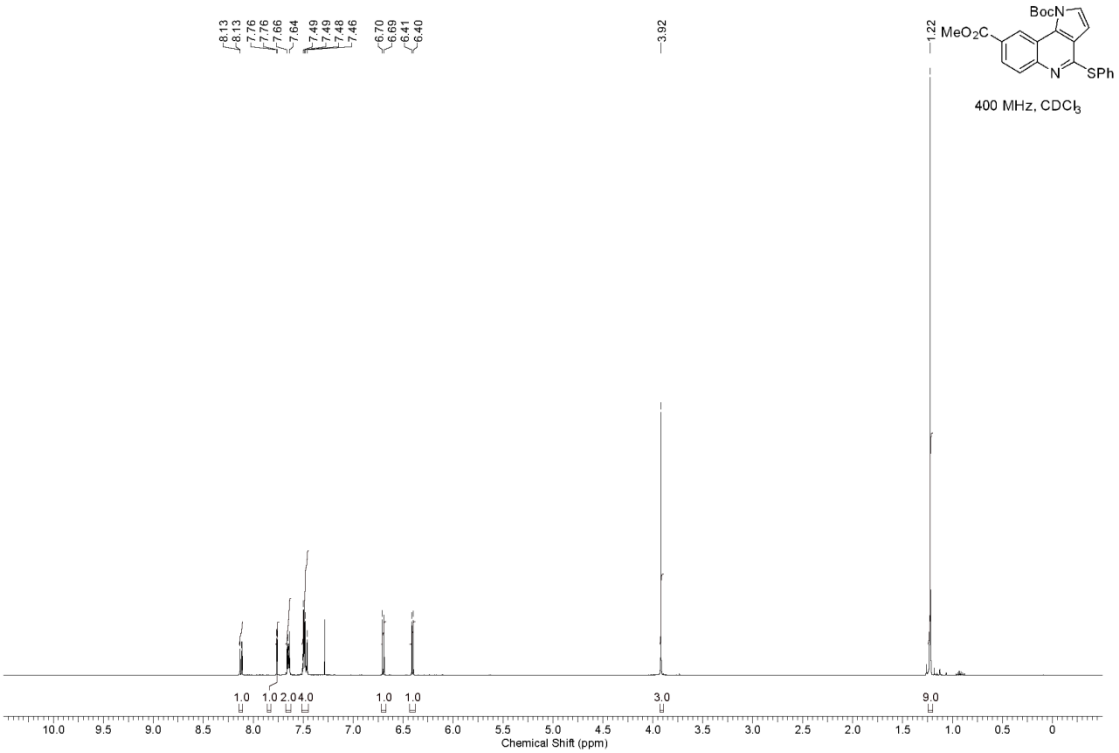


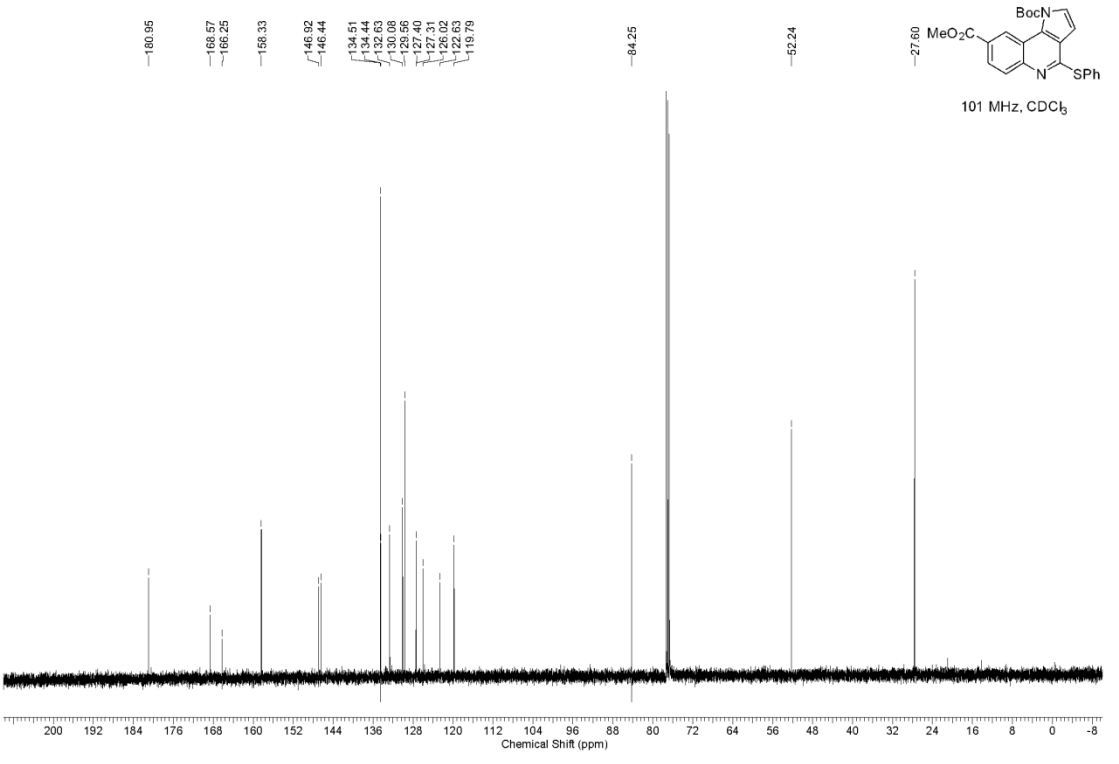
tert-Butyl 2-(5-(methoxycarbonyl)-2-(methyleneamino)phenyl)-1_H_-pyrrole-1-carboxylate (11)



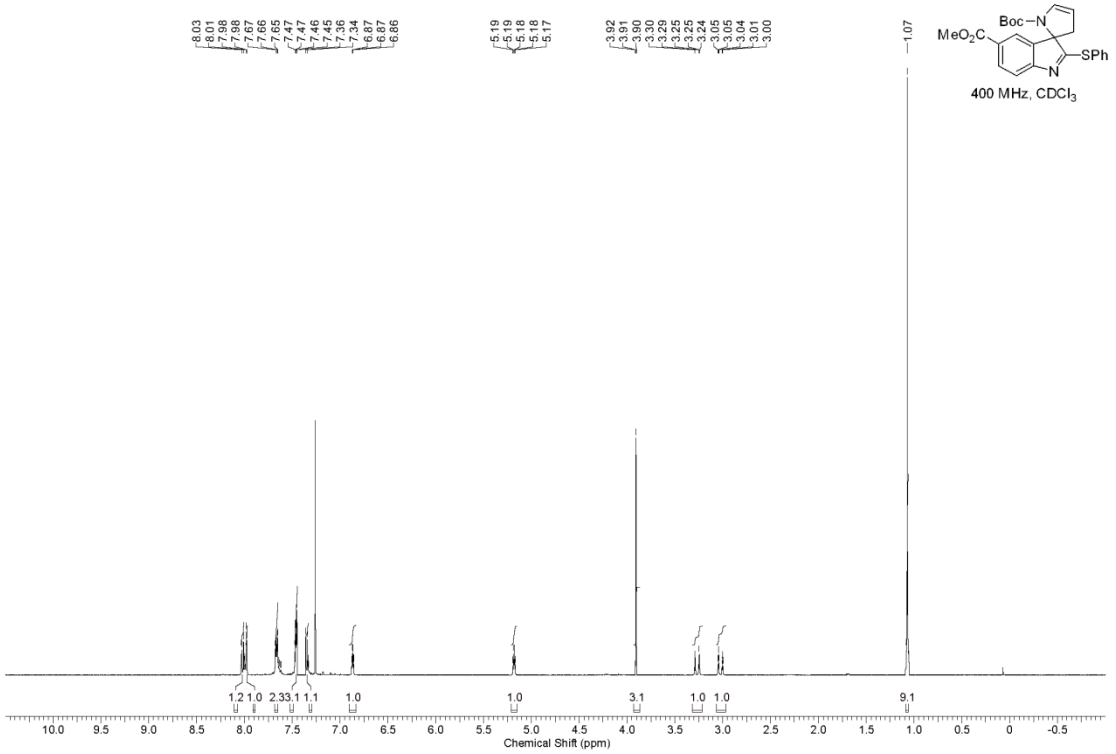


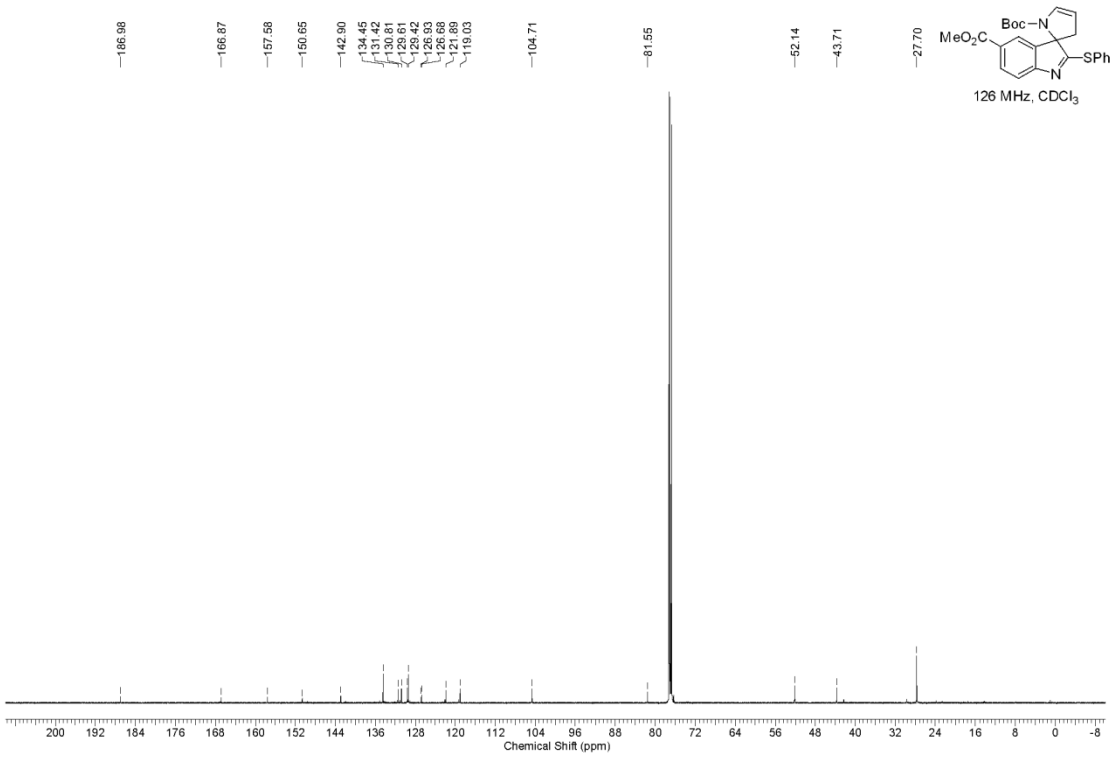
1-*tert*-butyl 8-methyl 4-(phenylthio)-1*H*-pyrrolo[3,2-c]quinoline-1,8(3aH,9bH)-dicarboxylate (8)





1'-(*tert*-butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(3'H)-dicarboxylate (9)





1'-(*tert*-Butyl) 5-methyl 2-(phenylthio)spiro[indole-3,2'-pyrrole]-1',5(5'H)-dicarboxylate (17)