Synthesis of Subsituted Isatins from MBH adduct of 1,5,6-trisubstituted Isatins using (2,4-dinitrophenyl)hydrazine and K10 Clay; Explored as Protection & De-protection Chemistry

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Supporting Information

1. EXPERIMENTAL DETAILS.

1.1. General Considerations

NMR spectra were recorded at 300 (^{1}H) and 75(^{13}C) MHz respectively on a Bruker Advance DPX-300 MHz NMR spectrometer. NMR spectra were obtained using chloroform-d_1 as solvent. Chemical shifts are given in δ-scale with tetramethylsilane as internal standard. Coupling constants (J) are reported in hertz (Hz). Yields refer to quantities obtained after chromatography. IR spectra were taken on Nicolet (Impact 400D FT-IR) spectrophotometer or Bomem MB-series FT-IR spectrophotometer. Abbreviations used in ^{1}H NMR are: s-singlet, d-doublet, dd-doublet of a doublet, brs-broad singlet, q-quartet and m-multiplet.

Analytical thin layer chromatography (TLC) was performed on glass plates coated with silica gel (Merck) containing 13% calcium sulphate as binder. Column chromatography was done using 100-(200 mesh silica gel and appropriate mixture of petroleum ether (60-80 $^{\circ}$c) and ethyl acetate was used as solvent system for elution unless otherwise specified. The solvents were removed (under reduced pressure where necessary) using Heidolph or Buchi rotary evaporator. All solvents were distilled prior to use and reactions requiring dry conditions were carried out using dry solvents which were dried according to the literature procedure.

Extraction of the reaction mixtures were done with the appropriate organic solvents, the extraction was repeated with fresh solvent at least three times before the organic layers were combined. Washing of the combined organic layer was also repeated three times in each case (distilled water, 0.2 N hydrochloric acid, saturated sodium bicarbonate solution, brine, *etc*. As required by the procedure).

1.2. General Experimental Procedure for *N*-alkylation of isatin:

A mixture of isatin (1 mmol), alkyl bromide/iodide (1.5 mmol) and calcium hydride (3 mmol) in DMF was stirred at 60 °C for 1 hour. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water then neutralized with 2N hcl and extracted using ethyl acetate. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired *N*-alkylisatin.

1.3. General Experimental Procedure for the preparation of MBH adducts of isatin (Protection of C-3 of isatin):

A mixture of *N*-alkylisatin (1 mol), 1.5 equiv. Of ethyl acrylate (1.5 mmol), 0.02 equiv. Of DABCO (0.02 mmol) in etoh (5 ml) was stirred at RT for 3-6 days. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate. The organic layer was washed successively with 0.2N HCl. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product obtained was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired MBH adduct of *N*-alkylisatin.

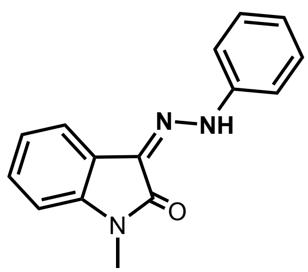
1.4. a) General procedure for C-C bond cleavage (de-protection of MBH adduct to phenylhydrazone):

(i) A mixture of MBH adduct 50 mg (0.20 mmol), 1.5 equivalent of 2,4-dinitrophenylhydrazine was made as a paste and was ground in a mortar-pestle in solvent free condition at room temperature (30 min). The crude reaction mixture was purified by silica gel column chromatography using EtOAc: hexane (20: 80) as eluent to afford the desired 3-(2-(2,4-dinitrophenyl)hydrazono)-1,5-dimethylindolin-2-one.

(ii) A mixture of 2,4-dinitrophenylhydrazone of MBH adduct of 1,5-dimethylisatin (0.05g, 0.20mmol), 100% w/w K-10 clay were added in Acetone (2.5 ml) and was stirred at RT for 30 minutes. After completion of the reaction (monitored by TLC), the reaction mixture was filtered to remove clay the filtrate was evaporated to get pure crystalline product of the desired 1,5-dimethylisatin (0.0376g) 85%.

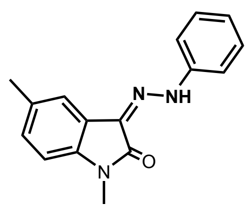
Spectral data for selected compounds

Compound 1b : 1-methyl-3-(2-phenylhydrazono)indolin-2-one:



1H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.28(s, 3H), 6.69 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.16-7.33 (m, 7H), 12.76 (s, NH); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.76, 109.24, 118.80, 122.73, 122.95, 124.93, 127.55, 127.79, 127.85, 128.40, 128.99, 133.42, 136.03, 143.60, 164.96; FAB mass: Calcd.For $C_{15}H_{13}N_3O$ Exact Mass: 251.11; Found m/e: 251.11.

Compound 2b : 1,5-dimethyl-3-(2-phenylhydrazono)indolin-2-one:



1H NMR ($CDCl_3$/TMS, 300.1 MHz): 2.38(s, 3H), 3.28(s, 3H), 6.70 (d, J = 8.2 Hz, 1H), 6.75-7.47 (m, 7H), 12.74 (s, NH); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 21.17, 25.48, 108.15, 114.25, 119.48, 121.23, 123.01, 127.18, 128.52, 129.40, 132.15, 138.94, 142.73, 162.36; FAB mass: Calcd.For$C_{16}H_{15}N_3O$: 265.12; Found m/e (M+1): 266.21.

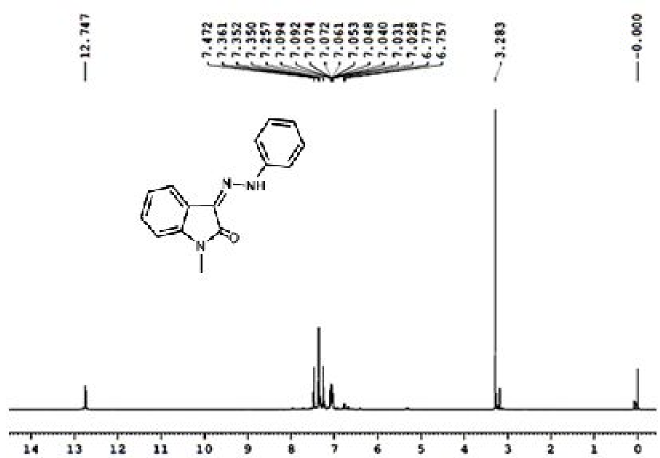


Figure S1: ^{1}H NMR for Compound 1b : 1-methyl-3-(2-phenylhydrazono)indolin-2-one:

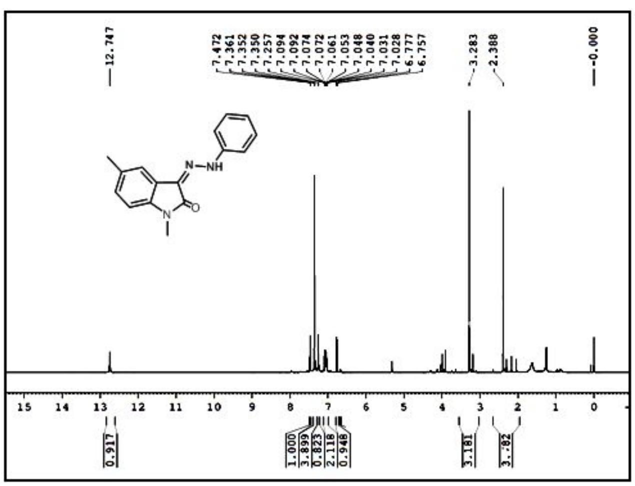


Figure S2: ^{1}H NMR for 1,5-dimethyl-3-(2-phenylhydrazono)indolin-2-one 2b

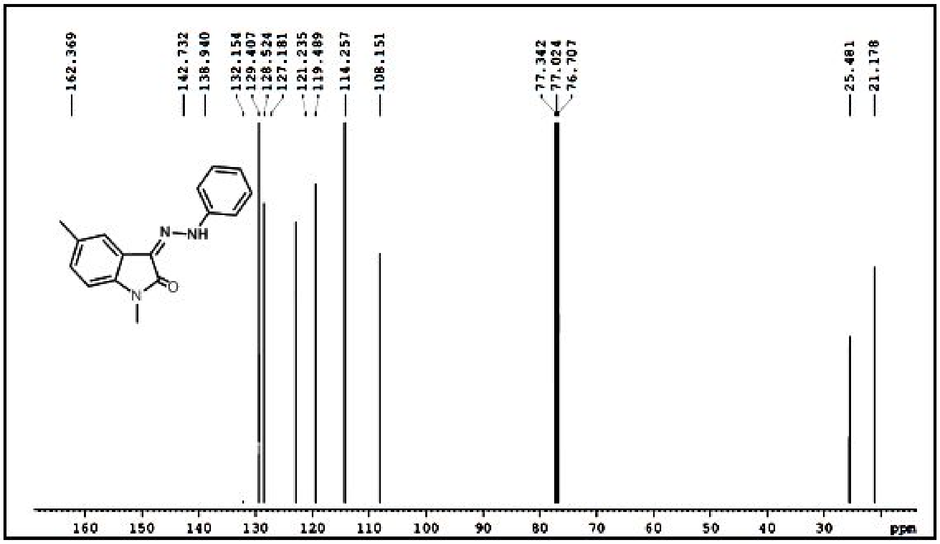


Figure S3: [13]C-NMR for 1,5-dimethyl-3-(2-phenylhydrazono)indolin-2-one 2b

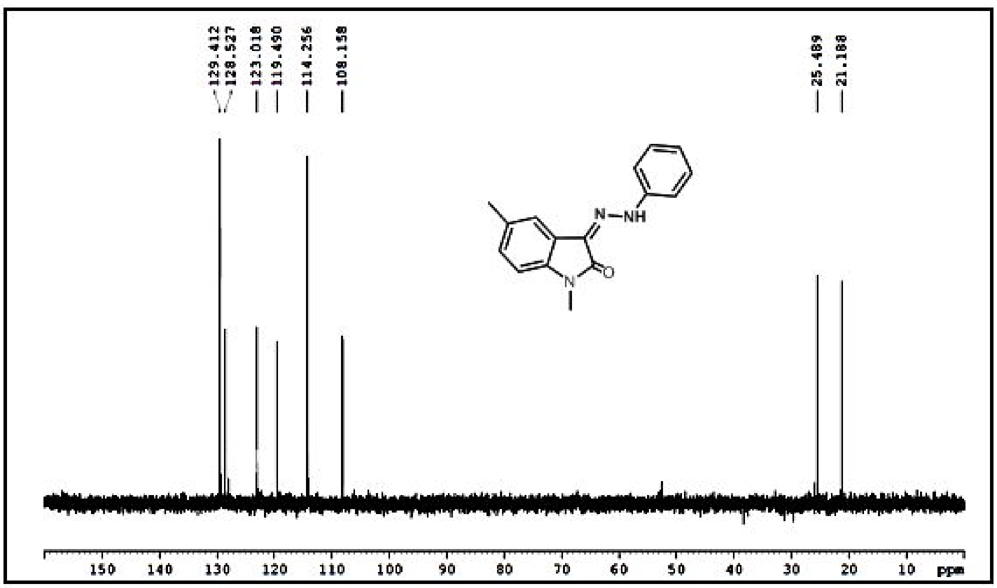


Figure S4: [13]C-NMR (DEPT-135) 1,5-dimethyl-3-(2-phenylhydrazono)indolin-2-one [2b]

UV-Visible spectroscopic comparison proof

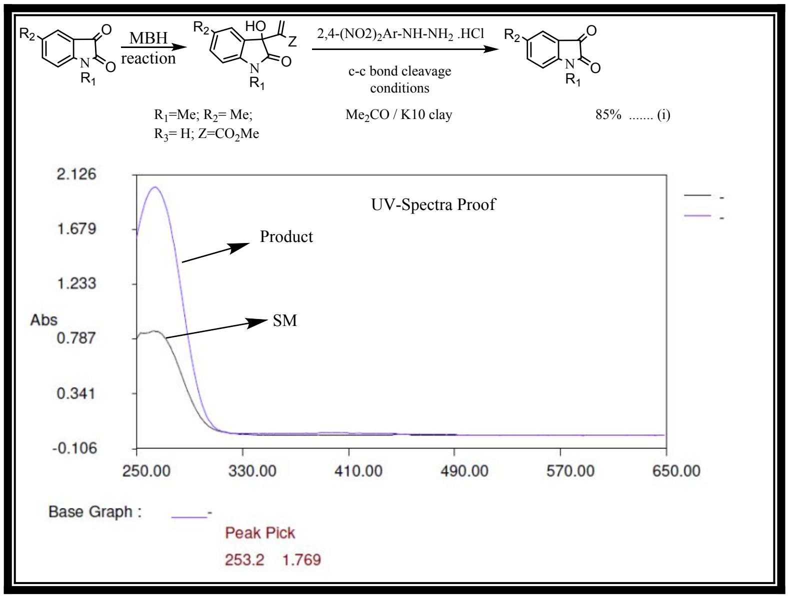
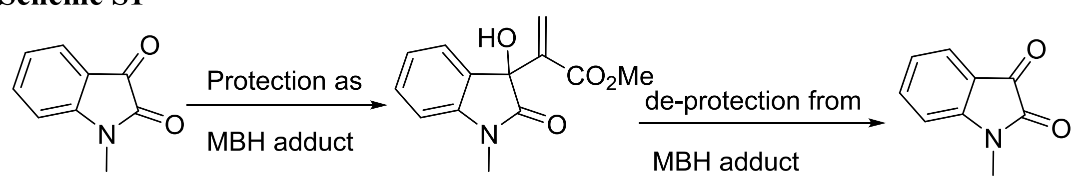


Figure S5: UV Spectrum of 1,5-dimethylindoline-2,3-dione, 3c

Scheme S1



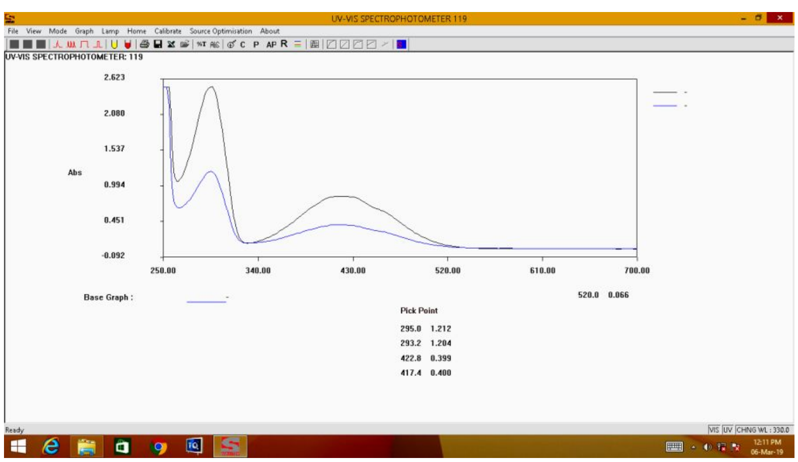
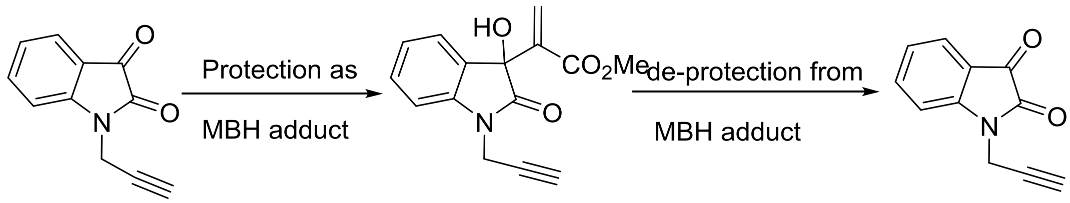


Figure S6: UV Spectrum of 1-methylindoline-2,3-dione, 2c:

Scheme S2



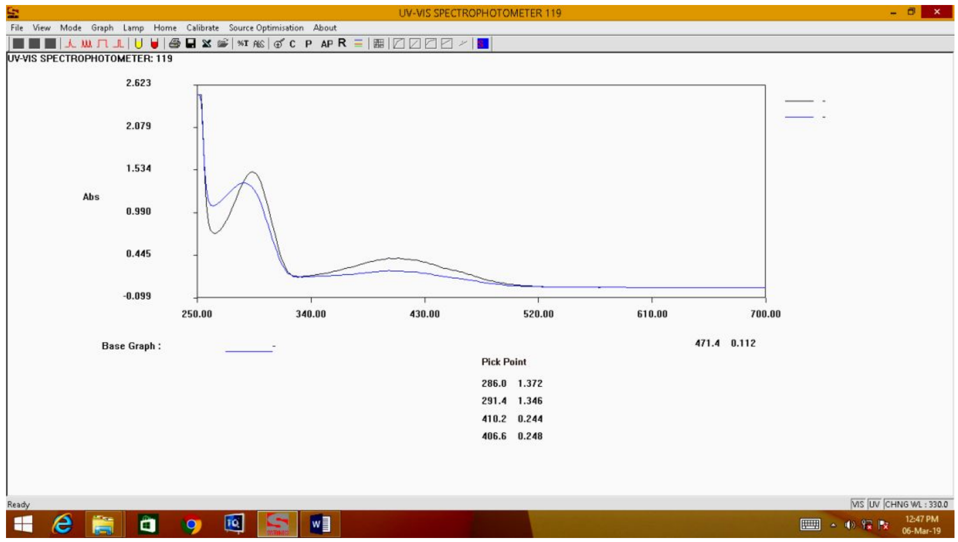
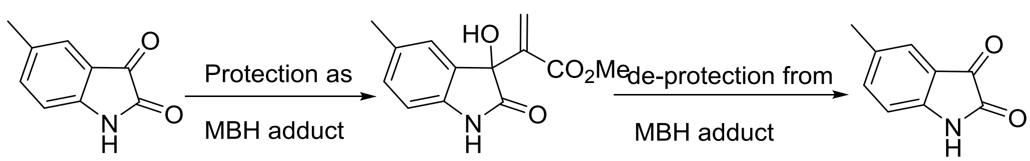


Figure S7: UV Spectrum of 1-(prop-2-yn-1-yl)indoline-2,3-dione, 4c:

Scheme S3



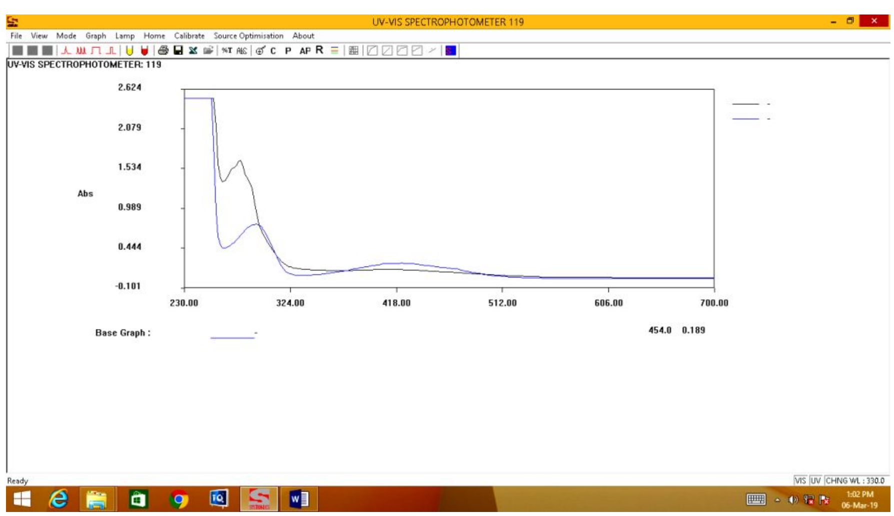
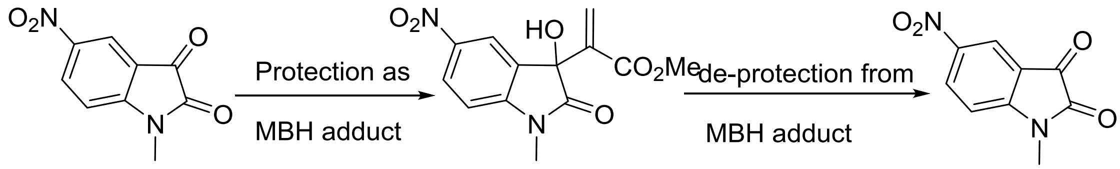


Figure S8: UV Spectrum of 5-dimethylindoline-2,3-dione, 3c:

Scheme S4



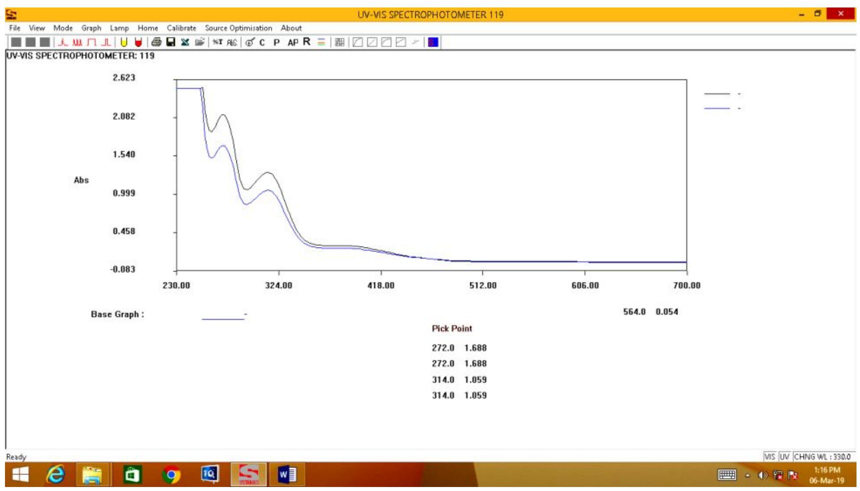
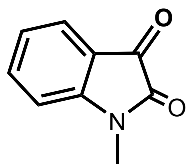


Figure S9: UV Spectrum of 1-methyl-5-nitroindoline-2,3-dione, 5c:

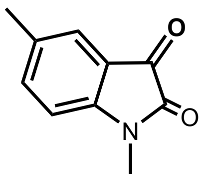
Spectral data for isatin after protection de-protection steps

1-methylindoline-2,3-dione, 2c:



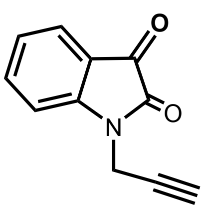
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.23 (s, 3H), 6.90 (d, *J* = 7.8 Hz, 1H, Ar), 7.02 (t, *J* = 7.8 Hz, 1H, Ar), 7.29 (t, *J* = 7.8 Hz, 1H, Ar), 7.36 (d, *J* = 7.8Hz, 1H, Ar); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.59, 117.8, 122.1, 124.9, 130.1, 135.4, 160.5, 178.8; FAB mass: Calcd.For $C_9H_7NO_2$ Exact Mass: 161.05; Found m/e: 161.17

1,5-dimethylindoline-2,3-dione, 3c:



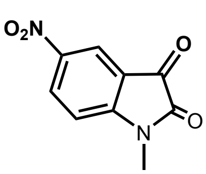
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.35 (s, 3H), 3.28 (s, 3H), 7.32 (d, *J*=6.8Hz, 1H), 7.59 (s, 1H), 7.71 (d, *J*=6.8Hz, 1H*)*; 13C NMR ($CDCl_3$/TMS, 75.3 MHz): 24.3, 30.5,117.7, 122.0, 130.4, 134.5, 135.1, 145.1, 160.4, 184.4; FAB mass: Calcd.For $C_{10}H_9NO_2$ Exact Mass: 175.06; Found m/e: 175.27

1-(prop-2-yn-1-yl)indoline-2,3-dione, 4c:



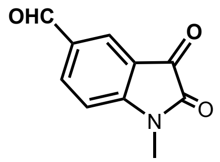
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.25 (t, *J*=2.4Hz, 1H), 4.57-4.62 (d, *J* = 2.4 Hz, 2H), 7.19(dt, *J*=7.0, 2.5Hz, 1H), 7.52(dt, *J*=7.0, 2.5Hz, 1H), 7.79 (dd, *J*=7.2, 2.5 Hz, 1H), 7.83 (dd, *J*=7.2, 2.5 Hz, 1H); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.6, 70.9, 78.1, 117.8, 122.1, 124.9, 130.1, 134.8, 148.1, 160.4, 184.4; FAB mass: Calcd.For $C_{11}H_7NO_2$ Exact Mass: 185.05; Found m/e: 185.11

1-methyl-5-nitroindoline-2,3-dione, 5c:



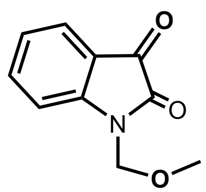
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ : 3.26 (s, 3H), 7.19 (d, *J*=6.7Hz, 1H), 8.02(s, 1H), 8.45(d, *J*=6.7Hz, 1H),); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.5, 118.7, 123.0, 125.0, 127.1, 144.5, 154.0, 160.4, 184.4 FAB mass: Calcd.For $C_9H_6N_2O_4$ Exact Mass: 206.03; Found m/e: 206.32

1-methyl-2,3-dioxoindoline-5-carbaldehyde, 6c:



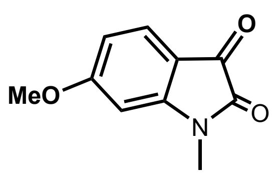
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ : 3.28(s, 3H), 6.99(d, 7.0Hz, 1H), 7.69 (d, *J*=2.4Hz, 1H), 7.86 (dd, *J*=2.4, 7.0Hz, 1H), 9.84(s, 1H); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.5, 123.9, 128.4, 130.6, 131.8, 138.7, 149.9, 164.3, 176.7, 190.7; FAB mass: Calcd.For $C_{10}H_7NO_3$ Exact Mass: 189.04; Found m/e: 189.12

1-(methoxymethyl)indoline-2,3-dione, 7c:



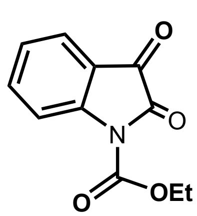
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.48 (s, 3H), 5.13 (d, *J* = 11.1 Hz, 1H), 5.17 (d, *J* = 11.1 Hz, 1H), 7.06-7.10 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 56.7, 71.4, 117.8, 122.1, 124.9, 130.1, 134.8, 48.1, 160.4, 184.4; FAB mass: Calcd.For $C_{10}H_9NO_3$ Exact Mass: 191.06; Found m/e: 191.13

6-methoxy-1-methylindoline-2,3-dione:



^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.28(s, 3H), 3.73(s, 3H), 6.87 (d, *J*=6.8Hz, 1H), 7.00 (s, 1H), 7.16 (d, *J*=7.0Hz, 1H); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.5, 55.9, 105.3, 110.1, 110.4, 131.1, 149.1, 160.4, 167.6, 183.2; FAB mass: Calcd.For $C_{10}H_9NO_3$ Exact Mass: 191.06; Found m/e: 191.12

Ethyl 2,3-dioxoindoline-1-carboxylate:



^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.30 (t, J=8.2Hz, 3H), 4.27(q, J=8.2Hz, 2H), 6.87(d, *J*=7.3Hz, 1H), 7.63(d, *J*=7.3Hz, 1H), 7.86 (dd, *J*=2.3, 7.2Hz, 1H), 7.86 (dd, *J*=2.3, 7.3Hz, 1H); 13C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 13.63, 61.66, 105.3, 120.1, 122.4, 131.1, 149.1, 156.7, 170.4, 177.6, 183.2; FAB mass: Calcd.For $C_{11}H_9NO_4$ Exact Mass: 219.05; Found m/e: 219.13

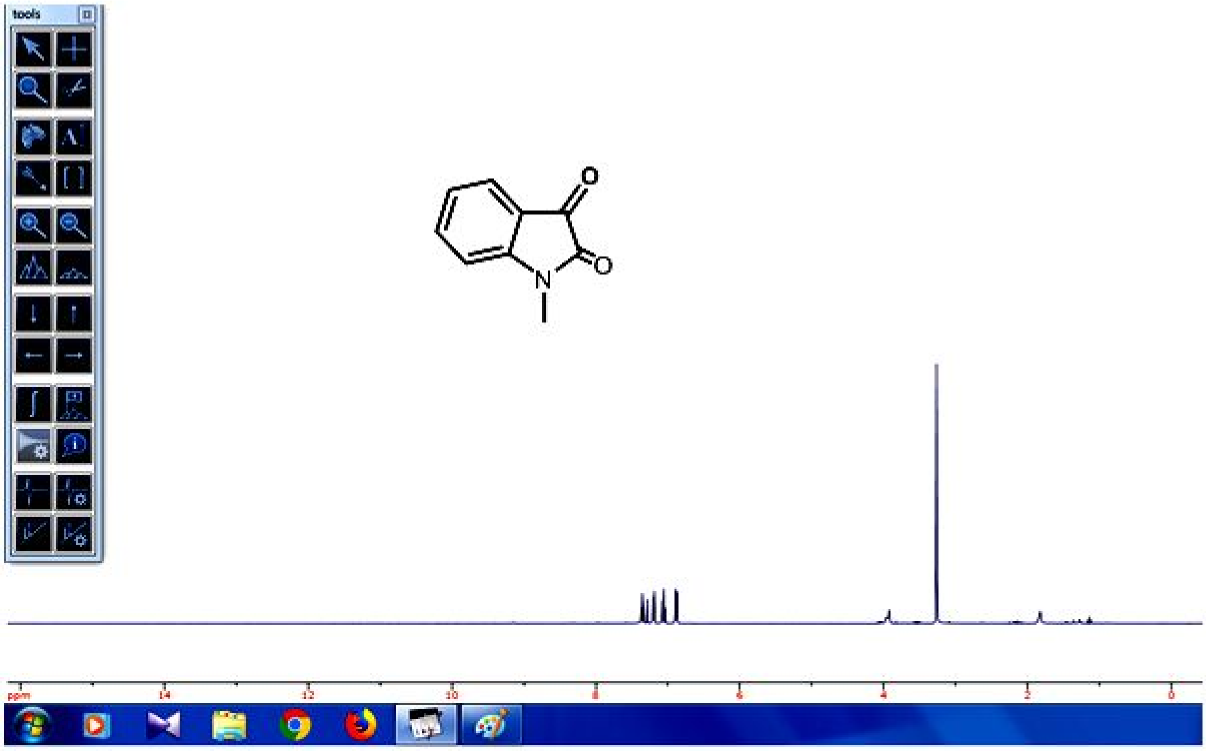


Figure S10: ^{1}H NMR for 1-methylindoline-2,3-dione, 2c:

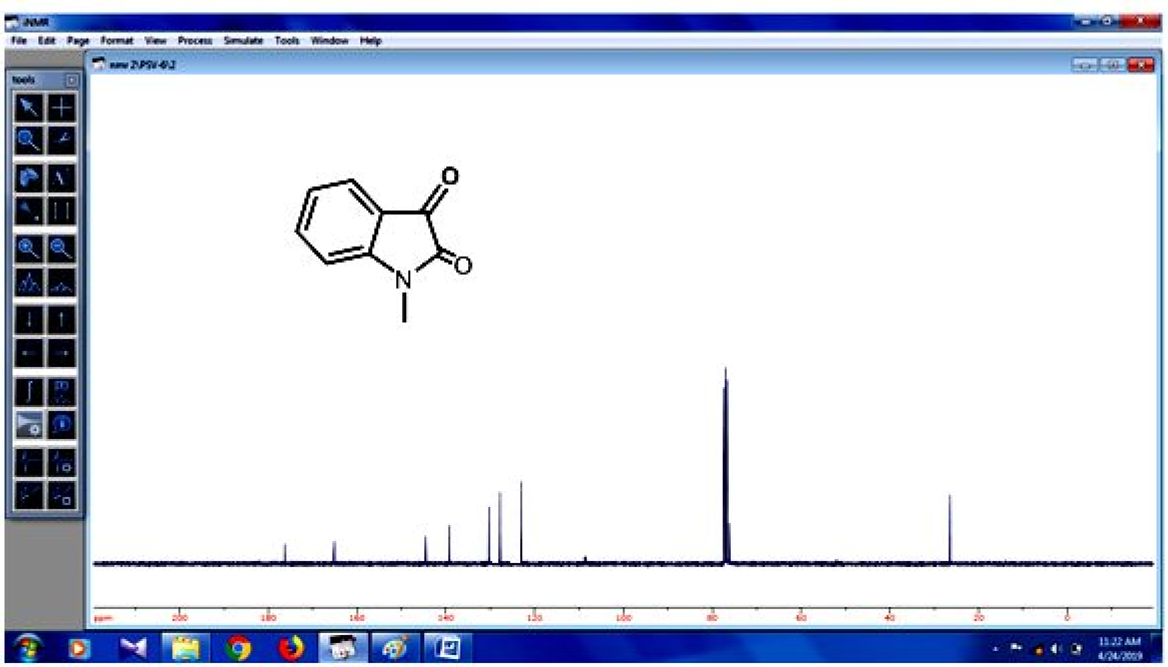


Figure S11: ^{13}C NMR for 1-methylindoline-2,3-dione, 2c:

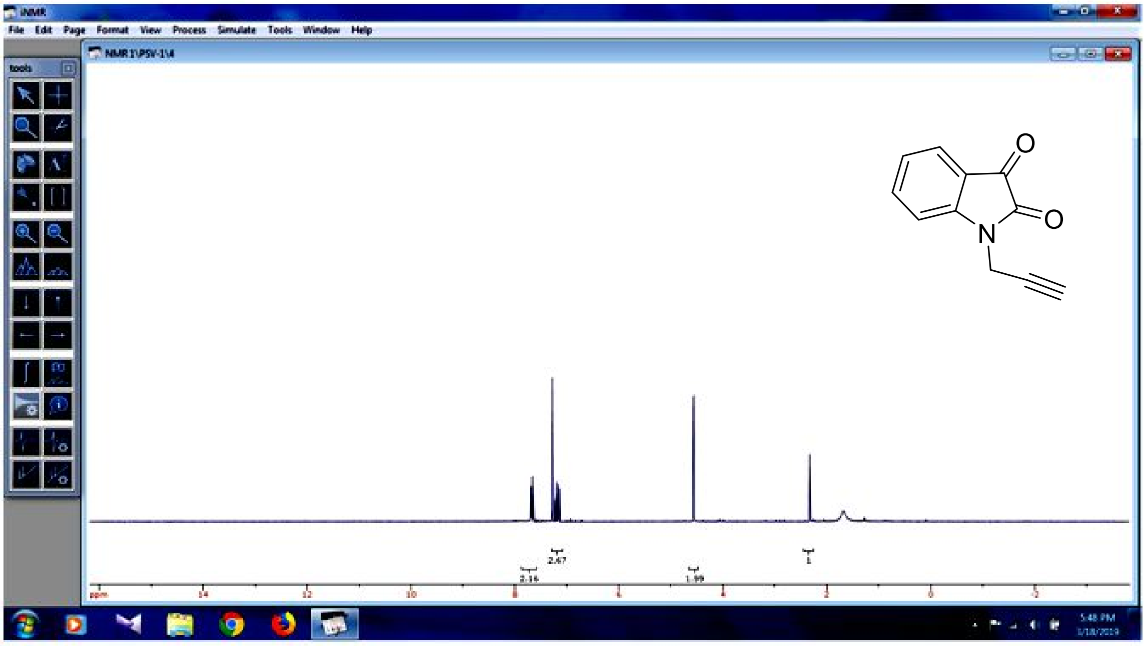


Figure S12: ^{1}H NMR for1-(prop-2-yn-1-yl)indoline-2,3-dione, 4c:

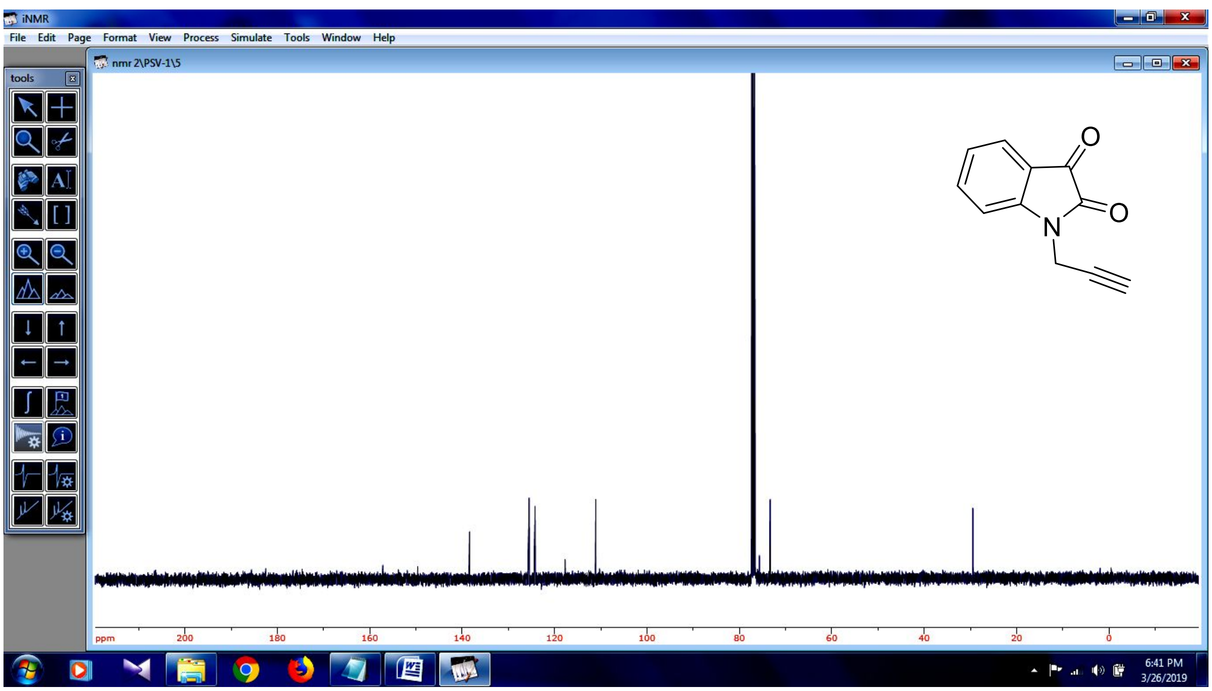


Figure S13: ^{13}C NMR for1-(prop-2-yn-1-yl)indoline-2,3-dione, 4c:

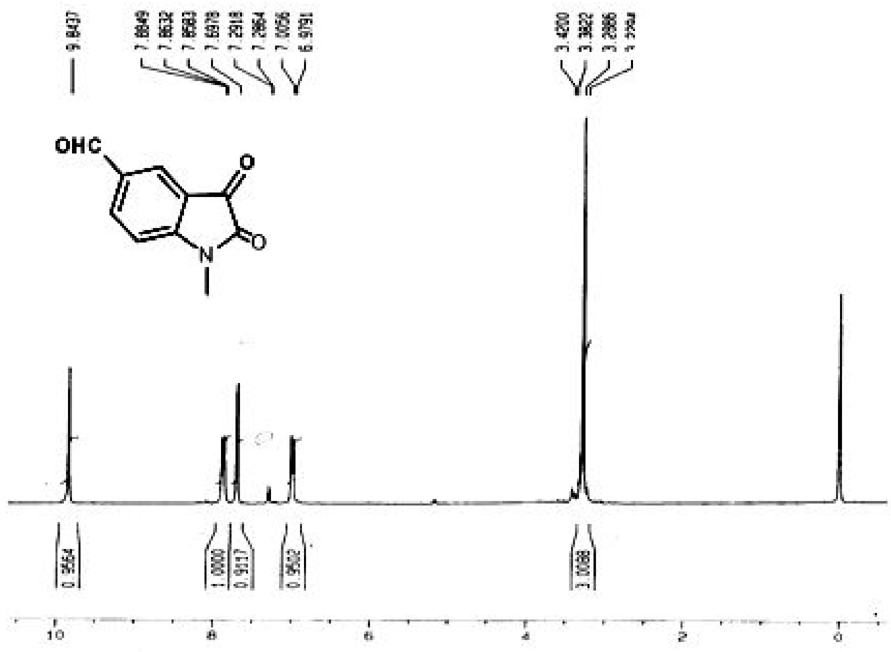


Figure S14: ^{1}H NMR for 1-methyl-2,3-dioxoindoline-5-carbaldehyde, 6c:

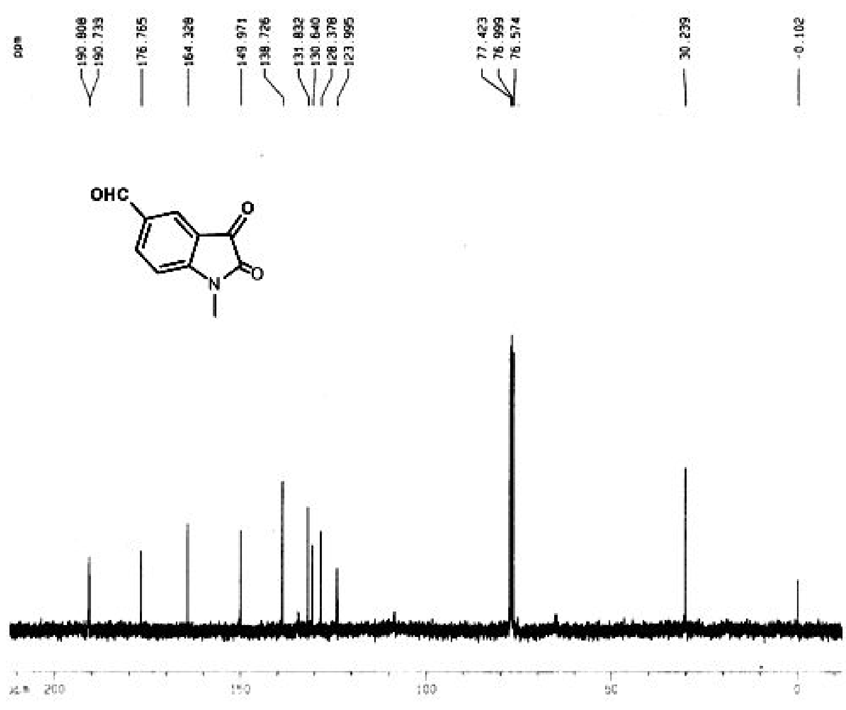


Figure S15: ^{13}C NMR for 1-methyl-2,3-dioxoindoline-5-carbaldehyde, 6c:

Figure S16: ¹H NMR for 6-methoxy-1-methylindoline-2,3-dione:

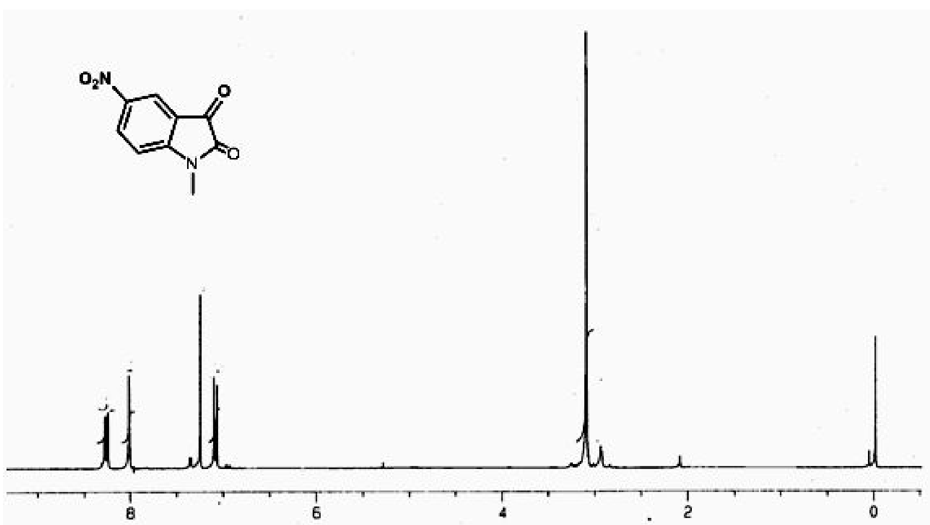


Figure S17: ¹H NMR for 1-methyl-5-nitroindoline-2,3-dione, 5c:

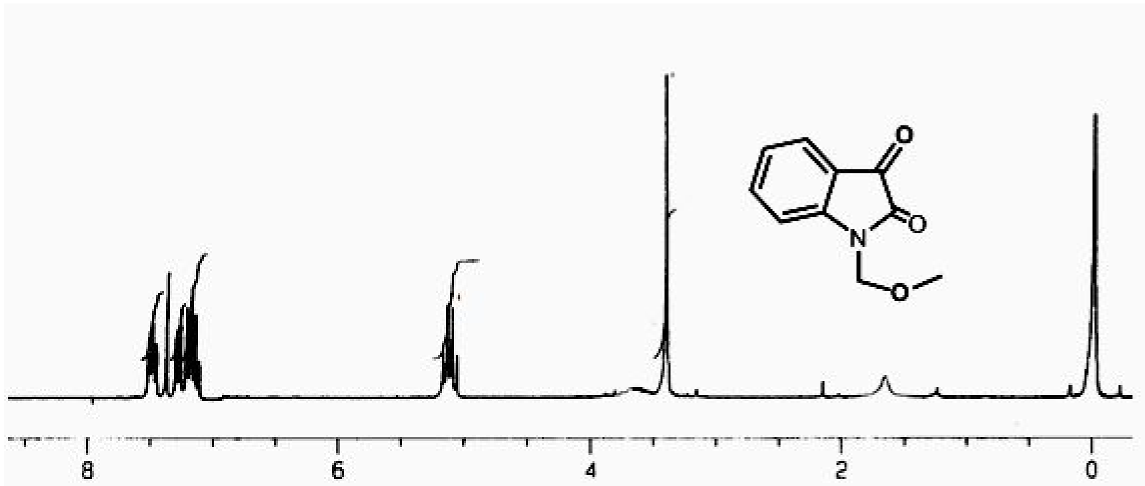


Figure S18: ¹H NMR for 1-(methoxymethyl)indoline-2,3-dione, 7c:

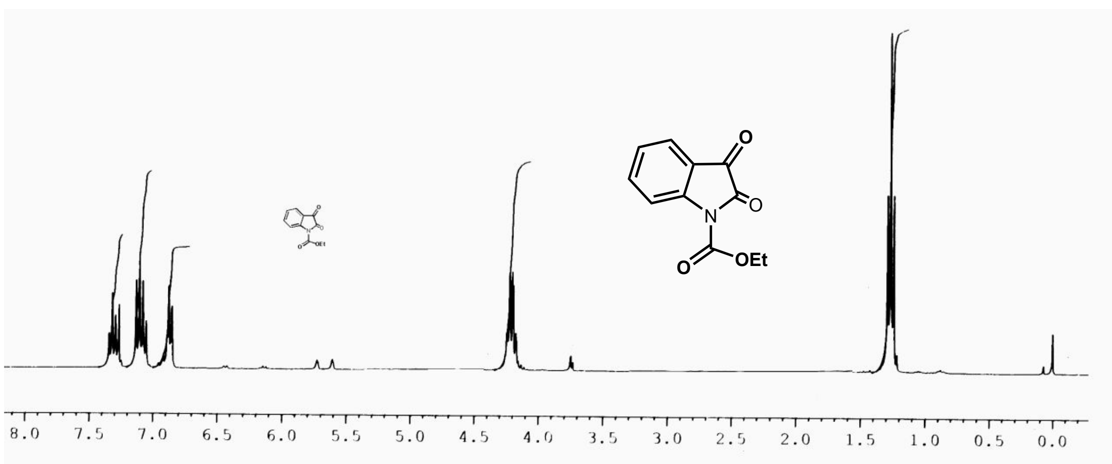


Figure S19: ¹H NMR for Ethyl 2,3-dioxoindoline-1-carboxylate: