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Full Paper

Synthesis of Indoxylic Acid Esters by Rhodium-catalyzed Carbene N–H Insertion and Thermal Cyclization

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Reaction between diethyl diazomalonate and a range of *N*-alkylanilines in the presence of a catalytic amount of rhodium(II) acetate dimer afforded carbene N–H insertion to produce anilinomalonates in modest-to-good yields. Upon heating to a high temperature for a short time, the anilinomalonates underwent thermal cyclization to indoxylic acid esters.

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Introduction

3-Indolinones, also known as indoxyls, are air-sensitive derivatives of indole. The parent indoxyl undergoes the well-known oxidative dimerization to give the blue dye indigo, together with the isomeric indorubicin as a by-product (Fig. 1).[1] Natural indigo, obtained from the plants *Indigofera tinctoria* and *Isatis tinctoria*, is formed via hydrolysis of indoxyl glycosides, such as indicane, followed by oxidation.[2] Other indoxyls, including adrenolutin, are metabolites of adrenaline,[3] whereas indoxyl acid esters (that exist exclusively in the 3-hydroxyindole tautomer) are pivotal intermediates in the synthesis of substituted indoxyl glycosides, which are important reagents in biochemistry and histochemistry for monitoring glycosidase enzyme activity.[4,5] We now report a simple new route to synthesizing indoxyl acid esters from anilines that employs carbene N–H insertion as a key step.

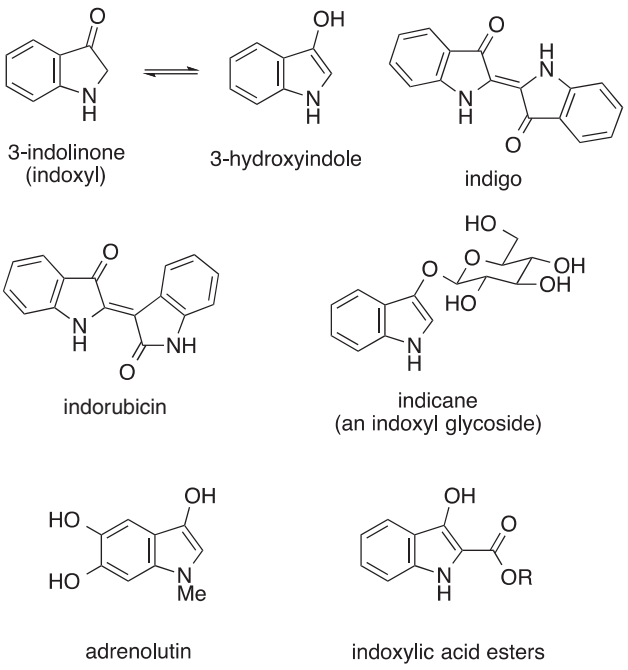


Fig. 1. Derivatives of 3-indolinone (indoxyl).

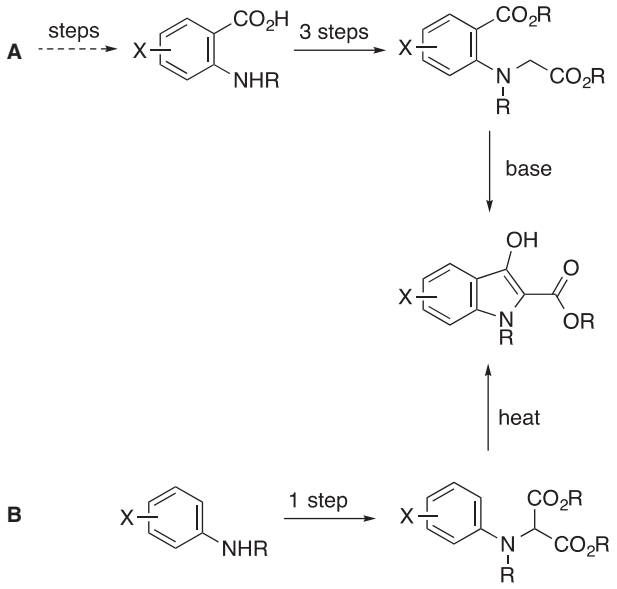
Results and Discussion

The most general route to indoxyl acid esters involves the intermediacy of *N*-(2-carboxyphenyl)glycine derivatives, obtained from the corresponding anthranilic acids (Scheme 1, Route **A**).[4,5] Although this is a relatively straightforward route, it can involve additional steps if the anthranilic acid is commercially unavailable. In contrast, our route involves readily accessible anilines as starting reagent, transforming into anilinomalonate derivatives, as outlined in Scheme 1, Route **B**. It was expected that the required anilinomalonates would be produced in a single-step method, involving carbene N–H insertion reactions of the corresponding anilines.

Thermal reaction of aniline with a diazocarbonyl compound, ethyl diazoacetate, was first described by Curtius over 100 years ago.[6] However, currently, the reaction is invariably carried out in the presence of a metal catalyst, based on Yates seminal report on copper-catalyzed decomposition of diazoacetophenone in the presence of aniline to give α-anilinoacetophenone in 33 % yield.[7] The N–H insertion reaction between anilines and diazocarbonyl compounds is now a standard reaction of carbene and metal carbene intermediates,[8,9] and is catalyzed by a range of transition metal complexes, including copper,[10–13] rhodium,[14–17] rhenium,[18] and ruthenium.[19] In our laboratory, we have used a rhodium-catalyzed carbene insertion reaction in the N–H bond of *N*-alkylanilines as a key step in a modified Bischler synthesis method for the preparation of indoles.[20–23] In continuation to this study and studies involving N–H insertion chemistry,[24–29] we now report the application of N–H insertion reactions for the synthesis of indoxyls.

The desired anilinomalonates were prepared by N–H insertion of the rhodium carbene derived from diethyl diazomalonate and a range of anilines **1** (Table 1). Two methods were used, both

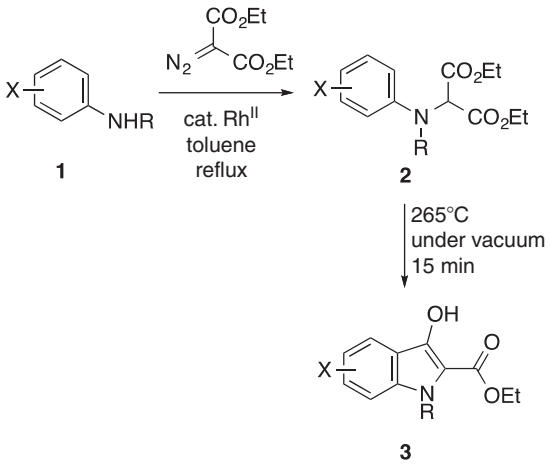
involving rhodium(II) acetate dimer as catalyst (2 mol-%), and entailed either heating the reaction mixture to reflux in toluene for 1.5–2.0 h or heating to 80°C in dichloromethane in a sealed tube in a focussed microwave reactor. This gave a range of anilinomalonates **2** in modest-to-good yields (53–82 %) (Table 1).



Scheme 1. Synthesis routes of indoxyl acid esters.

There are only three reports on the cyclization of anilinomalonates to indoxyl acid esters, typically generating poor yields. For example, heating diethyl anilinomalonate to 260–265°C under water aspirator vacuum produced ethyl 3-hydroxyindole-2-carboxylate in 40 % yield.[30] Likewise, an *N*-substituted derivative of dimethyl anilinomalonate only cyclized in 17 % yield upon heating,[31] although in the third report, in an approach to adrenolutin derivatives, the key cyclization step was reported to proceed in good yield upon brief heating (10 min) in paraffin at 240–245°C.[3] To this effect, we focussed on heating the anilinomalonates **2** to a relatively high temperature for a short time using microwave irradiation. A representative range of diethyl anilinomalonates **2**, incorporating both electron-donating and -withdrawing substituents, were heated in a focussed microwave reactor to a temperature set at 250°C. Although the cyclized product was sometimes isolated, yields varied considerably. Upon analysis of the microwave absorption trace for the duration of the reaction, it became evident that the maximum temperature attained in each sample was inconsistent. In an attempt to overcome this problem, 0.5 mL of solvent *N*-methylpyrrolidone was added and the reaction was repeated, but with no improvement. Likewise, the addition of acid catalysts, such as Amberlyst 15® and boron trifluoride etherate, to the reaction mixture did not induce cyclization. Because of the highly inconsistent results obtained under microwave irradiation conditions, we reverted to traditional heating. When the anilinomalonates were heated under vacuum to 265°C for 15 min, the desired ethyl 3-hydroxyindole-2-carboxylates were isolated (Table 1).

Table 1. Rhodium-catalyzed carbene N–H insertion reactions and thermal cyclization reactions



Compounds **1**/**2**	X	R	Yield of compounds **2** [%]	Compounds **3**	X	Yield of compounds **3** [%]
a	2-Br	Me	68[A]	**a**	7-Br	35
b	2-MeO	Me	69			
c	3-Br	Me	53			
d	4-Br	Me	58	**b**	5-Br	77
e	4-Cl	Me	76	**c**	5-Cl	74
f	4-Cl	PMB[B]	82	**d**	5-Cl	43
g	4-MeO	Me	71	**e**	5-MeO	55
h	4-Me	Me	71			
i	4-NO_2	Me	75			
j	4-CO_2Me	Me	75	**f**	5-CO_2Me	62

[A]Reaction was carried out in dichloromethane at 80°C in a microwave reactor (300 W, 20 min).
[B]PMB = *p*-methoxybenzyl.

The reaction was compatible with a range of substituents located at varying positions in the aromatic ring, and moderate-to-good yields of 3-hydroxyindole esters were obtained. In an attempt to achieve a one-pot synthesis of 3-hydroxyindoles, 4-chloro-*N*-methylaniline (**1e**), diethyl 2-diazomalonate, and rhodium(II) acetate in toluene were heated to 110°C for 2 h. The reaction mixture was then cooled to room temperature and the solvent was removed. The residue was then heated to 265°C for 15 min under vacuum to produce 3-hydroxyindole (**3c**) in 33 % yield. As the combined yield of **3c** obtained via two separate reactions was higher than that obtained via the one-pot reaction (i.e. 56 % vs 33 %), the one-pot approach was not pursued.

In conclusion, we have developed a simple, two-step route to synthesizing indoxyl acid esters from anilines using rhodium-catalyzed carbene N–H insertion followed by thermal cyclization of intermediate anilinomalonates.

Experimental

General Procedures

Commercially available reagents were used throughout without purification unless otherwise stated. Light petroleum refers to the fraction with bp 40–60°C. Ether refers to diethyl ether. Analytical thin layer chromatography was carried out on aluminium-backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm. Column chromatography was carried out on silica gel cartridges (50 µm silica) with a Jones Chromatography Flashmaster II automated system. Fully characterized compounds are chromatographically homogeneous. Infrared spectra were recorded in the range 4000–600 cm^{-1}. NMR spectra were recorded on Bruker instruments at 300, 400, and 500 MHz (^1H frequencies) and 75, 100, and 125 MHz (^{13}C frequencies). Chemical shifts are reported in ppm and are referenced to residual H in the deuterated solvent as the internal standard. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, and CH_3 groups were assigned from the distortionless enhancement by polarization transfer (DEPT) spectra. High- and low-resolution mass spectra were recorded on a Bruker Microtof time-of-flight mass spectrometer. Microwave reactions were carried out in a CEM Discover™ S-class (300 W) microwave reactor with an infrared temperature sensor.

Diethyl Diazopropanedioate

To diethyl malonate (4.0 g, 25.0 mmol) in acetonitrile (200 mL) at 0°C was added 4-acetamidobenzenesulfonyl azide (7.2 g, 30.0 mmol). Triethylamine (7.0 mL, 49.9 mmol) was added dropwise to the stirred reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the yellow–white residue was triturated with chloroform. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was purified over a silica cartridge (100 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The title compound was isolated as a yellow oil (3.2 g, 70 %). ν_{max} (neat)/cm^{-1} 2985, 2134, 1757, 1733, 1688, 1467, 1448, 1395, 1371, 1313, 1266, 1197, 1170, 1073, 1016. δ_H ($CDCl_3$, 400 MHz) 4.31 (4H, q, *J* 7.0, OCH_2CH_3), 1.32 (6H, t, *J* 7.2, OCH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 161.1 (C), 61.6 (CH_2), 14.3 (Me); diazo carbon was not observed. Data are consistent with the literature.[32]

4-Chloro-N-(4-methoxyphenyl)methylaniline (**1f**)

To 4-chloroaniline (1.02 g, 8.00 mmol) and *para*-methoxybenzaldehyde (1.09 g, 8.00 mmol, 1 eq.) in tetrahydrofuran (10 mL) was added glacial acetic acid (0.46 mL, 8.00 mmol, 1 eq.). The reaction mixture was sealed and heated to 65°C for 1 h. The solution was then cooled to room temperature and sodium borohydride (0.45 g, 12.00 mmol, 1.5 eq.) was added. The reaction mixture was re-sealed and stirred at room temperature for 48 h. The solution was neutralized with aqueous sodium hydroxide and the organic material was extracted in dichloromethane. The solvent was removed under reduced pressure and the colourless solid was purified over a silica cartridge (100 g) using a solvent system of 0–100 % ethyl acetate in cyclohexane over a period of 40 min. The title compound **1f** was isolated as a fluffy colourless solid (1.35 g, 68 %), mp 75–76°C (lit. 78–81°C[33]). ν_{max} (neat)/cm^{-1} 3410, 1595, 1495, 1476, 1401, 1308, 1246, 1173, 1028. δ_H ($CDCl_3$, 400 MHz) 7.28 (2H, d, *J* 8.8, ArH), 7.12 (2H, d, *J* 8.8, ArH), 6.89 (2H, d, *J* 8.8, ArH), 6.56 (2H, *J* 8.8, ArH), 4.24 (2H, d, *J* 4.2, CH_2), 3.98 (1H, br s, NH), 3.82 (3H, s, OMe). δ_C ($CDCl_3$, 100 MHz) 158.9 (C), 146.7 (C), 130.9 (C), 129.0 (CH), 128.7 (CH), 122.0 (C), 114.1 (CH), 113.9 (CH), 55.3 (Me), 47.8 (CH_2).

Diethyl 2-[N-(2-Bromophenyl)-N-methylamino] propanedioate (**2a**)

To 2-bromo-*N*-methylaniline (223 mg, 1.20 mmol) and diethyl diazopropanedioate (246 mg, 1.32 mmol, 1.1 eq.) in dichloromethane (4 mL) was added rhodium(II) acetate dimer (2 mol-%). The reaction vessel was sealed and the reaction mixture heated in a focussed microwave reactor (300 W) to 80°C for 20 min. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified over silica using a solvent system of 15 % ethyl acetate in light petroleum to give the *title compound* **2a** as a colourless oil (281 mg, 68 %). ν_{max} ($CHCl_3$)/cm^{-1} 2941, 1733, 1587, 1476, 1445, 1305, 1258, 1178, 1115, 1028. δ_H ($CDCl_3$, 400 MHz) 7.57 (1H, dt, *J* 7.6, 0.9, ArH), 7.29–7.27 (2H, m, ArH), 6.95 (1H, ddd, *J* 8.0, 5.8, 3.0, ArH), 4.84 (1H, s, $CH(CO_2Et)_2$), 4.31–4.25 (4H, m, CH_2CH_3), 3.05 (3H, s, NMe), 1.32 (6H, t, *J* 7.1, CH_2CH_3). δ_C ($CDCl_3$,100 MHz) 167.5 (C), 149.3 (C), 133.8 (CH), 127.9 (CH), 124.9 (CH), 123.6 (CH), 119.1 (C), 68.6 (CH), 61.5 (CH_2), 36.5 (Me), 14.2 (Me). Found: $M+Na^+$ 366.0315. $C_{14}H_{18}{}^{79}BrNO_4+Na^+$ requires 366.0317.

Diethyl 2-[N-(2-Methoxyphenyl)-N-methylamino] propanedioate (**2b**)

To 2-methoxy-*N*-methylaniline (137 mg, 1.00 mmol) and diethyl diazopropanedioate (242 mg, 1.30 mmol) in toluene (3 mL) under an atmosphere of nitrogen was added rhodium(II) acetate dimer (9 mg, 0.02 mmol), and the mixture was heated to 110°C for 2 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2b** was isolated as a colourless oil (203 mg, 69 %). ν_{max} (neat)/cm^{-1} 2981, 1732, 1595, 1502, 1458, 1368, 1295, 1260, 1235, 1206, 1173, 1152, 1132, 1101, 1025. δ_H ($CDCl_3$, 400 MHz) 7.05 (1H, dd, *J* 7.8, 1.8, ArH), 7.00–6.89 (2H, m, ArH), 6.85 (1H, dd, *J* 7.8, 1.5, ArH), 5.07 (1H, s, $CH(CO_2Et)_2$), 4.30–4.23 (4H, m, OCH_2CH_3), 3.84 (3H, s, NMe), 3.02 (3H, s, OMe), 1.29 (6H, t, *J* 7.2, OCH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 168.4 (C), 151.5 (C), 139.9 (C), 122.7 (CH),

120.9 (CH), 119.7 (CH), 111.5 (CH), 67.6 (CH), 61.3 (CH_2), 55.5 (Me), 35.9 (Me), 14.2 (Me). Found: M+H^+ 296.1486. $C_{15}H_{21}NO_5$+H^+ requires 296.1498.

*Diethyl 2-[N-(3-Bromophenyl)-N-methylamino] propanedioate (**2c**)*

To 3-bromo-*N*-methylaniline (186 mg, 1.00 mmol) and diethyl diazopropanedioate (242 mg, 1.30 mmol) in toluene (3 mL) under an atmosphere of nitrogen was added rhodium(II) acetate dimer (9 mg, 0.02 mmol). The reaction mixture was heated to 110°C for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2c** was isolated as a colourless oil (182 mg, 53 %). ν_{max} (neat)/cm^{-1} 2982, 1735, 1592, 1560, 1489, 1446, 1367, 1300, 1217, 1175, 1158, 1117, 1096, 1025. δ_H ($CDCl_3$, 400 MHz) 7.09 (1H, t, *J* 8.5, ArH), 6.94–6.92 (2H, m, ArH), 6.71 (1H, d, *J* 8.5, ArH), 5.06 (1H, s, C*H*($CO_2Et)_2$), 4.29 (4H, q, *J* 7.0, OCH_2CH_3), 3.05 (3H, s, NMe), 1.31 (6H, t, *J* 7.2, OCH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.2 (C), 150.2 (C), 130.4 (CH), 123.4 (C), 121.4 (CH), 116.4 (CH), 111.8 (CH), 65.7 (CH), 62.0 (CH_2), 35.9 (Me), 14.1 (Me). Found: C 48.8, H 5.1, N 4.0. $C_{14}H_{18}BrNO_4$ requires C 48.9, H 5.3, N 4.1 %. Found: M+H^+ 344.0483. $C_{14}H_{18}{}^{79}BrNO_4$+$H^+$ requires 344.0497.

*Diethyl 2-[N-(4-Bromophenyl)-N-methylamino] propanedioate (**2d**)*

To 4-bromo-*N*-methylaniline (223 mg, 1.20 mmol) and diethyl diazopropanedioate (246 mg, 1.32 mmol, 1.1 eq.) in toluene (2 mL) was added rhodium(II) acetate dimer (2 mol-%). The reaction vessel was sealed and heated to 110°C for 1.5 h. The solvent was removed under reduced pressure and the residue purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2d** was isolated as a pale yellow oil (240 mg, 58 %). ν_{max} (neat)/cm^{-1} 2982, 1735, 1591, 1495, 1366, 1603, 1273, 1216, 1174, 1158, 1113, 1026. δ_H ($CDCl_3$, 400 MHz) 7.34 (2H, d, *J* 9.0, ArH), 6.68 (2H, d, *J* 9.0, ArH), 5.04 (1 H, s, C*H*($CO_2Et)_2$), 4.28 (4H, q, *J* 7.2, CH_2CH_3), 3.04 (3H, s, NMe), 1.30 (6H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.3 (C), 148.0 (C), 131.9 (CH), 115.1 (CH), 110.73 (C), 66.0 (CH), 62.0 (CH_2), 36.0 (Me), 14.1 (Me). Found: C 49.0, H 5.1, N 4.0. $C_{14}H_{18}BrNO_4$ requires C 48.9, H 5.3, N 4.1 %. Found: M+H^+ 344.0486. $C_{14}H_{18}{}^{79}BrNO_4$+$H^+$ requires 344.0497.

*Diethyl 2-[N-(4-Chlorophenyl)-N-methylamino] propanedioate (**2e**)*

To 4-chloro-*N*-methylaniline (100 mg, 0.71 mmol) and diethyl diazopropanedioate (158 mg, 0.85 mmol, 1.2 eq.) in toluene (1 mL) was added rhodium(II) acetate dimer (2 mol-%). The reaction vessel was sealed and heated to 110°C for 1.5 h. The solvent was removed under reduced pressure and the residue purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2e** was isolated as a very pale yellow oil (160 mg, 76 %). ν_{max} (neat)/cm^{-1} 2983, 1735, 1597, 1475, 1447, 1337, 1303, 1273, 1216, 1174, 1158, 1113, 1026. δ_H ($CDCl_3$, 400 MHz) 7.20 (2H, d, *J* 9.2, ArH), 6.73 (2H, d, *J* 9.2, ArH), 5.04 (1H, s, C*H*($CO_2Et)_2$), 4.28 (4H, q, *J* 7.2, CH_2CH_3), 1.30 (6H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.4 (C), 147.6 (C), 129.0 (CH), 123.6 (C), 114.7 (CH), 66.1 (CH), 62.0 (CH_2), 36.0 (Me), 14.1 (Me). Found: C 55.8, H 5.8, N 4.6. $C_{14}H_{18}ClNO_4$ requires C 56.1, H 6.1, N 4.7 %. Found: M+H^+ 300.0996. $C_{14}H_{18}{}^{35}ClNO_4$+$H^+$ requires 300.1003.

*Diethyl 2-[N-(4-Chlorophenyl)-N-(4-methoxybenzyl) amino]propanedioate (**2f**)*

To 4-chloro-*N*-(4-methoxybenzyl)aniline (37 mg, 0.15 mmol) and diethyl diazopropanedioate (34 mg, 0.18 mmol, 1.2 eq.) in toluene (1 mL) was added rhodium(II) acetate dimer (2 mol-%). The reaction mixture was sealed and heated to 110°C for 2 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified over silica using a solvent system of 20 % ethyl acetate in light petroleum. The *title compound* **2f** was isolated as a yellow solid (50 mg, 82 %), mp 86–88°C. ν_{max} ($CHCl_3$)/cm^{-1} 2939, 1737, 1612, 1599, 1512, 1500, 1464, 1370, 1303, 1246, 1175, 1101, 1034. δ_H ($CDCl_3$, 400 MHz) 7.23 (2H, d, *J* 8.7, ArH), 7.12 (2H, d, *J* 9.1, ArH), 6.84 (2H, d, *J* 8.7, ArH), 6.70 (2H, d, *J* 9.1, ArH), 5.11 (1H, s, C*H*CO_2Et), 4.62 (2H, s, CH_2Ar), 4.23–4.12 (4H, m, CH_2CH_3), 3.79 (3H, s, OMe), 1.22 (6H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.5 (C), 158.6 (C), 146.9 (C), 130.2 (C), 128.9 (CH), 127.8 (CH), 124.1 (C), 116.0 (CH), 113.8 (CH), 66.4 (CH), 62.0 (CH_2), 55.2 (Me), 53.6 (CH_2), 14.0 (Me).

*Diethyl 2-[N-(4-Methoxyphenyl)-N-methylamino] propanedioate (**2g**)*

To 4-methoxy-*N*-methylaniline (137 mg, 1.00 mmol) and diethyl diazopropanedioate (242 mg, 1.30 mmol, 1.3 eq.) in toluene (3 mL) under an atmosphere of nitrogen was added rhodium(II) acetate dimer (2 mol-%). The reaction mixture was sealed and heated to 110°C for 2 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min to give the title compound **2g** as a yellow oil (209 mg, 71 %). ν_{max} (neat)/cm^{-1} 2983, 1734, 1512, 1465, 1446, 1369, 1298, 1241, 1176, 1156, 1112, 1028. δ_H ($CDCl_3$, 400 MHz) 6.86–6.80 (4H, m, ArH), 4.99 (1H, s, C*H*($CO_2Et)_2$), 4.27 (4H, q, *J* 7.2, CH_2CH_3), 3.77 (3H, s, NMe), 3.03 (3H, s, OMe), 1.29 (6H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.8 (C), 153.0 (C), 143.6 (C), 116.0 (CH), 114.6 (CH), 67.3 (CH), 61.7 (CH_2), 55.7 (Me), 36.2 (Me), 14.1 (Me). The compound was previously reported,[34] but with no characterization data. Found: M+H^+ 296.1489. $C_{15}H_{21}NO_5$+H^+ requires 296.1498.

*Diethyl 2-[N-Methyl-N-(4-methylphenyl)amino] propanedioate (**2h**)*

To *N*,4-dimethylaniline (145 mg, 1.20 mmol) and diethyl diazopropanedioate (246 mg, 1.32 mmol) in toluene (2 mL) was added rhodium(II) acetate dimer (11 mg, 0.02 mmol). The reaction vessel was sealed and heated to 110°C for 1.5 h. The solvent was removed under reduced pressure and the residue purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2h** was isolated as a light opaque oil (238 mg, 71 %). ν_{max} ($CHCl_3$)/cm^{-1} 2982, 1735, 1617, 1519, 1447, 1366, 1302, 1275, 1205, 1156, 1112, 1027. δ_H ($CDCl_3$, 400 MHz) 7.07 (2H, d, *J* 8.6, ArH), 6.74 (2H, d, *J* 8.6, ArH), 5.08 (1H, s, C*H*($CO_2Et)_2$), 4.27 (4H, q, *J* 7.2, OCH_2CH_3), 3.05 (3H, s, NMe), 2.26 (3H, s, PhCH_3), 1.30 (6H, t, *J* 7.2, OCH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.8 (C), 146.9 (C), 129.7 (CH), 127.9 (C), 113.8 (CH), 66.4 (CH), 61.7 (CH_2), 35.8 (Me), 20.3 (Me), 14.1 (Me). Found: M+H^+ 280.1543. $C_{15}H_{22}NO_4$+H^+ requires 280.1549.

*Diethyl 2-[N-Methyl-N-(4-nitrophenyl)amino] propanedioate (**2i**)*

To *N*-methyl-4-nitroaniline (183 mg, 1.20 mmol) and diethyl diazopropanedioate (246 mg, 1.32 mmol) in toluene (2 mL) was added rhodium(II) acetate dimer (11 mg, 0.02 mmol). The reaction vessel was sealed and heated to 110°C for 1.5 h. The solvent was removed under reduced pressure and the residue purified over a silica cartridge (20 g) using a solvent system of 0–100 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **2i** was isolated as a yellow oil (278 mg, 75 %). ν_{max} (neat)/cm^{-1} 2983, 1736, 1594, 1504, 1386, 1368, 1322, 1295, 1224, 1200, 1177, 1105, 1023. δ_H ($CDCl_3$, 400 MHz) 8.17 (2H, d, *J* 9.5, ArH), 6.77 (2H, d, *J* 9.5, ArH), 5.19 (1H, s, C*H*(CO_2Et)$_2$), 4.32 (4H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.17 (3H, s, NMe), 1.33 (6H, t, *J* 7.2, OCH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 166.4 (C), 153.5 (C), 126.0 (CH), 111.7 (CH), 71.9 (C), 65.3 (CH), 62.5 (CH_2), 36.5 (Me), 14.1 (Me). Found: C 53.6, H 5.7, N 8.4. $C_{14}H_{18}N_2O_6$ requires C 54.2, H 5.8, N 9.0 %.

*Diethyl 2-[N-(4-Methoxycarbonylphenyl)-N-methylamino]propanedioate (**2j**)*

To methyl 4-(methylamino)benzoate (198 mg, 1.20 mmol) and diethyl diazopropanedioate (246 mg, 1.32 mmol, 1.1 eq.) in toluene (2 mL) was added rhodium(II) acetate dimer (2 mol-%). The reaction vessel was sealed and heated to 110°C for 1.5 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified over a silica cartridge (20 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min to give the *title compound* **2j** as a light yellow oil (303 mg, 75 %). ν_{max} (neat)/cm^{-1} 2984, 1737, 1708, 1604, 1521, 1435, 1367, 1273, 1221, 1186, 1110, 1025. δ_H ($CDCl_3$, 400 MHz) 7.94 (2H, d, *J* 9.0, ArH), 6.77 (2H, d, *J* 9.0, ArH), 5.19 (1H, s, C*H*(CO_2Et)$_2$), 4.30 (4H, q, *J* 7.2, C*H*$_2$CH$_3$), 3.87 (3H, s, NMe), 3.12 (3H, s, CO_2C*H*$_3$), 1.31 (6H, t, *J* 7.2, CH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 167.0 (C), 167.0 (C), 152.3 (C), 131.3 (CH), 119.6 (C), 111.9 (CH), 65.3 (CH), 62.2 (CH_2), 51.7 (Me), 36.0 (Me), 14.1 (Me). Found: M+H$^+$ 324.1439. $C_{16}H_{21}NO_6$+H$^+$ requires 324.1447.

*Ethyl 7-Bromo-3-hydroxy-1-methyl-1H-indole-2-carboxylate (**3a**)*

Diethyl 2-[*N*-(2-bromophenyl)-*N*-methylamino]propanedioate (**2a**) (40 mg, 0.12 mmol) was heated under vacuum to 265°C for 15 min. The crude product was cooled to room temperature and purified over silica using a solvent system of 20 % ethyl acetate in light petroleum to give the *title compound* **3a** as a colourless solid (12 mg, 35 %), mp 118–120°C. ν_{max} ($CHCl_3$)/cm^{-1} 2986, 1713, 1655, 1612, 1571, 1540, 1509, 1446, 1412, 1384, 1351, 1271, 1240, 1170, 1096, 1020. δ_H ($CDCl_3$, 400 MHz) 8.73 (1H, s, OH), 7.70 (1H, d, *J* 7.7, ArH), 7.55 (1H, d, *J* 7.7, ArH), 6.91 (1H, t, *J* 7.7, H-5), 4.49 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 4.26 (3H, s, NMe), 1.47 (3H, t, *J* 7.2, CH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 164.0 (C), 148.5 (C), 134.9 (C), 132.7 (CH), 120.2 (CH), 119.7 (CH), 111.3 (C), 104.5 (C), 77.2 (C), 61.1 (CH_2), 34.1 (Me), 14.4 (Me). Found: M+Na$^+$ 319.9884. $C_{12}H_{12}{}^{79}BrNO_3$+Na$^+$ requires 319.9898.

*Ethyl 5-Bromo-3-hydroxy-1-methyl-1H-indole-2-carboxylate (**3b**)*

Diethyl 2-[*N*-(4-bromophenyl)-*N*-methylamino]propanedioate (**2d**) (36 mg, 0.11 mmol) was heated to 265°C under vacuum for 15 min. The crude product was cooled to room temperature and purified over a silica cartridge (10 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min to give the *title compound* **3b** as a very pale yellow solid (24 mg, 77 %), mp 115–117°C. ν_{max} ($CHCl_3$)/cm^{-1} 3332, 2938, 1736, 1665, 1608, 1567, 1539, 1495, 1470, 1439, 1370, 1339, 1273, 1194, 1148, 1111, 1051, 1019. δ_H ($CDCl_3$, 400 MHz) 8.54 (1H, s, OH), 7.89 (1H, d, *J* 2.0, H-4), 7.44 (1H, dd, *J* 8.9, 2.0, H-6), 7.15 (1H, d, *J* 8.9, H-7), 4.48 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 3.87 (3H, s, NMe), 1.46 (3H, t, *J* 7.2, CH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 136.0 (C), 131.8 (C), 130.0 (CH), 122.6 (CH), 117.8 (C), 111.9 (C), 111.4 (CH), 110.3 (C), 77.2 (C), 60.9 (CH_2), 31.9 (Me), 14.5 (Me). Found: C 48.3, H 4.0, N 4.6. $C_{12}H_{12}BrNO_3$ requires C 48.3, H 4.1, N 4.7 %. Found: M+Na$^+$ 319.9894. $C_{12}H_{12}{}^{79}BrNO_3$+Na$^+$ requires 319.9898.

*Ethyl 5-Chloro-3-hydroxy-1-methyl-1H-indole-2-carboxylate (**3c**)*

Diethyl 2-[*N*-(4-chlorophenyl)-*N*-methylamino]propanedioate (**2e**) (34 mg, 0.11 mmol) was heated to 265°C under vacuum for 15 min. The crude product was cooled to room temperature and purified over a silica cartridge (10 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **3c** was isolated as a colourless solid (21 mg, 74 %), mp 127–129°C. ν_{max} ($CHCl_3$)/cm^{-1} 2986, 1711, 1658, 1617, 1574, 1542, 1502, 1446, 1426, 1375, 1276, 1259, 1153, 1101, 1069, 1021. δ_H ($CDCl_3$, 400 MHz) 8.53 (1H, s, OH), 7.72 (1H, d, *J* 2.0, H-4), 7.31 (1H, dd, *J* 9.0, 2.0, H-6), 7.19 (1H, d, *J* 9.0, H-7), 4.48 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 3.88 (3H, s, NMe), 1.46 (3H, t, *J* 7.2, CH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 135.8 (C), 129.0 (C), 127.5 (CH), 124.7 (C), 119.4 (CH), 117.1 (C), 113.4 (C), 111.1 (CH), 77.2 (C), 60.9 (CH_2), 31.9 (Me), 14.5 (Me). Found: M+Na$^+$ 276.0399. $C_{12}H_{12}{}^{35}ClNO_3$+Na$^+$ requires 276.0403.

*Ethyl 5-Chloro-3-hydroxy-1-(4-methoxybenzyl)-1H-indole-2-carboxylate (**3d**)*

Diethyl 2-[*N*-(4-chlorophenyl)-*N*-(4-methoxybenzyl)amino] propanedioate (**2f**) (8.7 mg, 0.025 mmol) was heated under vacuum to 265°C for 15 min. The crude product was cooled to room temperature and purified over silica using a solvent system of 50 % dichloromethane in light petroleum to give the *title compound* **3d** as a colourless oil (3.2 mg, 43 %). ν_{max} ($CHCl_3$)/cm^{-1} 3010, 1745, 1674, 1613, 1514, 1479, 1441, 1370, 1348, 1302, 1250, 1177, 1143, 1111, 1072, 1034, 1014. δ_H ($CDCl_3$, 400 MHz) 8.65 (1H, s, OH), 7.75 (1H, d, *J* 2.0, H-4), 7.29 (1H, dd, *J* 9.0, 2.0, H-6), 7.21 (1H, d, *J* 9.0, H-7), 6.93 (2H, d, *J* 8.8, ArH), 6.78 (2H, d, *J* 8.8, ArH), 5.51 (2H, s, NC*H*$_2$Ar), 4.40 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 3.76 (3H, s, OMe), 1.34 (3H, t, *J* 7.2, CH$_2$C*H*$_3$). δ_C ($CDCl_3$, 100 MHz) 158.8 (C), 135.8 (C), 130.1 (C), 127.9 (CH), 127.3 (CH), 125.0 (C), 119.6 (CH), 117.6 (C), 116.5 (C), 114.0 (CH), 111.6 (CH), 109.9 (C), 77.2 (C), 61.0 (CH_2), 55.2 (Me), 47.7 (CH_2), 14.3 (Me). Found: M+K$^+$ 398.0765. $C_{19}H_{18}{}^{35}ClNO_4$+K$^+$ requires 398.0561.

*Ethyl 3-Hydroxy-5-methoxy-1-methyl-1H-indole-2-carboxylate (**3e**)*

Diethyl 2-[*N*-(4-methoxyphenyl)-*N*-methylamino]propanedioate (**2g**) (34 mg, 0.11 mmol) was heated to 265°C under vacuum for 15 min. The crude product was cooled to room temperature and purified over a silica cartridge (10 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min to give the *title compound* **3e** as a colourless solid (15 mg, 55 %), mp 114–116°C. ν_{max} ($CHCl_3$)/cm^{-1} 1706, 1655, 1627, 1545, 1447, 1429, 1381, 1289, 1272, 1240, 1182, 1133, 1096, 1047, 1022. δ_H ($CDCl_3$, 400 MHz) 8.58 (1H, s, OH), 7.17 (1H, d, *J* 9.2,

H-7), 7.12 (1H, d, *J* 2.4, H-4), 7.06 (1H, dd, *J* 9.2, 2.4, H-6), 4.47 (2H, q, *J* 7.2, CH_2CH_3), 3.86 (6H, s, NMe+OMe), 1.46 (3H, t, *J* 7.2, CH_2CH_3). δ_C ($CDCl_3$, 125 MHz) 153.4 (C), 147.8 (C), 133.5 (C), 119.3 (CH), 115.9 (C), 111.0 (CH), 110.0 (C), 99.4 (CH), 77.2 (C), 60.7 (CH_2), 55.7 (Me), 31.8 (Me), 14.5 (Me). Found: $M+Na^+$ 272.0898. $C_{13}H_{15}NO_4+Na^+$ requires 272.0899.

*2-Ethyl 5-Methyl 3-hydroxy-1-methyl-1H-indole-2,5-dicarboxylate (**3f**)*

Diethyl 2-[*N*-(4-methoxycarbonylphenyl)-*N*-methylamino] propanedioate (**2j**) (34 mg, 0.11 mmol) was heated to 265°C under vacuum for 15 min. The crude product was cooled to room temperature and purified over a silica cartridge (10 g) using a solvent system of 0–50 % ethyl acetate in cyclohexane over a period of 20 min. The *title compound* **3f** was isolated as a colourless solid (18 mg, 62 %), mp 122–124°C. ν_{max} ($CHCl_3$)/cm^{-1} 3323, 2990, 2953, 1705, 1657, 1615, 1573, 1553, 1481, 1437, 1382, 1346, 1302, 1270, 1240, 1191, 1146, 1110, 1090, 1039, 1019. δ_H ($CDCl_3$, 400 MHz) 8.69 (1H, s, OH), 8.55 (1H, d, *J* 1.8, H-4), 8.05 (1H, dd, *J* 9.0, 1.8, H-6), 7.27 (1H, d, *J* 9.0, H-7), 4.49 (2H, q, *J* 7.0, CH_2CH_3), 3.94 (3H, s, Me), 3.92 (3H, s, Me), 1.47 (3H, t, *J* 7.0, CH_2CH_3). δ_C ($CDCl_3$, 100 MHz) 167.4 (C), 139.1 (C), 127.8 (CH), 123.8 (CH), 121.2 (C), 116.2 (C), 110.5 (C), 109.5 (CH), 77.2 (C), 71.9 (C), 61.0 (CH_2), 51.9 (Me), 32.0 (Me), 14.5 (Me). Found: $M+Na^+$ 300.0841. $C_{14}H_{15}{}^{35}ClNO_5+Na^+$ requires 300.0848.

Supplementary Material

Copies of NMR spectra are available on the Journal's website.

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