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A palladium-catalyzed synthesis of isatins (1*H*-Indole-2,3-diones) from 1-(2-haloethynyl)-2-nitrobenzenes

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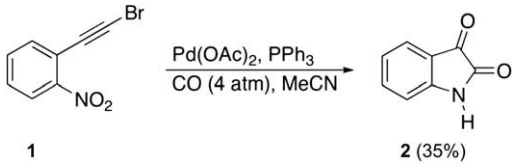
ABSTRACT

An inherently regiospecific synthesis of isatins (1*H*-indole-2,3-diones) starting from 1-halo-2-nitrobenzenes is described. The isatins are formed by an intramolecular palladium-catalyzed annulation of 2-(2-haloethynyl)-1-nitrobenzenes via the formation of 2-haloisatogens.

1. Introduction

Palladium-catalyzed N-heteroannulation of 2-(1-alken-1-yl)-1-nitrobenzenes using carbon monoxide as the ultimate reducing agent has emerged as a viable method for the synthesis of a variety of indoles.[1] In an attempt to expand the scope of this reaction to new substrates, 1-(2-bromoethynyl)-2-nitrobenzene (**1**) was reacted with carbon monoxide in the presence of a catalytic amount of palladium diacetate and triphenyl phosphine (Scheme 1). The starting material was completely consumed within one hour at 70 °C and a new product was observed by TLC. The product was identified as isatin (**2**) after chromatographic purification.



1 **2** (35%)

Scheme 1.

Isatin was first prepared independently by Erdman[2] and Laurent[3] in 1840 by oxidation of indigo. Isatins are important building blocks in organic synthesis[4] and a significant number of methods have been reported for their preparation.[5] Reaction of benzeneamines with chloral hydrate followed by treatment with sulfuric acid, a method developed by Sandmayer, is probably the most frequently used isatin synthesis.[6] Significant drawbacks are the highly acidic reaction conditions and the formation of regioisomeric isatins from annulation of 3-substituted benzeneamines. Isatins substituted in the 4- or 6-position have been prepared by transformation of 2-oxindole to the corresponding 3,3-dihalo-2-oxindole followed by hydrolysis.[7,8]

Based on the significant interest in isatins as synthetic building blocks, we decided to in more detail examine the reaction depicted in Scheme 1. Herein is described a regiospecific route to substituted isatins and the isolation of haloisatogens as intermediates.

2. Results and discussion

Optimization of the annulation conditions to form isatin (**2**) was initially examined and the results are summarized in Table 1. The reaction is probably palladium(II)-catalyzed since reaction of **1** using bis(dibenzylidenacetone)palladium(0)-triphenyl phosphine under a carbon monoxide atmosphere in acetonitrile only produced an intractable black solid (entry 2). Carbon monoxide was not required for the reaction to proceed (entry 4). Benzoquinone was added as an oxidant (entries 5–7) in case palladium(II) was reduced to palladium(0) during the course of the reaction. The highest yield was obtained using THF as the solvent in the presence of benzoquinone. Two other palladium catalysts, bis(acetonitrile) palladiumdichloride ($PdCl_2(MeCN)_2$) and bis(triphenylphosphine) palladiumdichloride ($PdCl_2(PPh_3)_2$), and a selection of solvents were also examined. Although **2** was formed in almost all cases, the product was frequently contaminated and we were unable to obtain a pure sample. A clean product under milder reaction conditions were realized using $PdCl_2(PPh_3)_2$ in acetone at ambient temperature (entry 15). The influence of the halogen on the yield of isatin was examined next. Reaction of the 2-(2-chloroethynyl)-1-nitrobenzene (**3**) produced **2** in a similar yield to the reaction of **1** (entry 17). However, a substantially improved yield was obtained from 1-(2-iodoethynyl)-2-nitrobenzene (**4**) (entry 18). The reaction time could be substantially reduced and the yield of **2** was somewhat improved (entry 19) performing the reaction at an elevated temperature (60 °C). Based on the results shown in Table 1, iodoalkynes were selected as the substrate of choice using $PdCl_2(PPh_3)_2$ in acetone either at ambient temperature or at 60 °C in all other examples discussed below. It should be noted that a small amount

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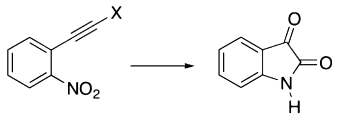
Table 1
Optimization of the reaction conditions



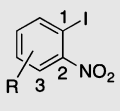
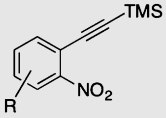
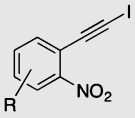
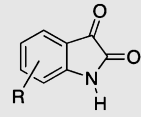
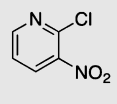
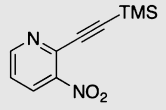
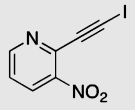
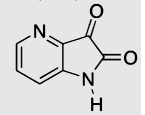
Entry	X	Solvent[a]	Catalyst (mol %)	Additive	Temp	Time	Yield[b]
1	Br	MeCN	$Pd(OAc)_2$ (10)	PPh_3 (40 mol %), CO (4 atm)	70 °C	1 h	35%
2	Br	MeCN	$Pd(dba)_2$ (10)	PPh_3 (40 mol %), CO (4 atm)	70 °C	1 h	
3	Br	MeCN	$Pd(OAc)_2$ (10)	CO (4 atm)	70 °C	1 h	11%
4	Br	MeCN	$Pd(OAc)_2$ (10)	—	70 °C	4.5 h	<22%[c]
5	Br	MeCN	$Pd(OAc)_2$ (10)	Benzoquinone (100 mol %)	70 °C	4 h	<43%[c]
6	Br	MeCN	$Pd(OAc)_2$ (1)	Benzoquinone (100 mol %)	70 °C	22 h	7%
7	Br	THF	$Pd(OAc)_2$ (10)	Benzoquinone (100 mol %)	70 °C	3.5 h	52%
8	Br	THF	$Pd(OAc)_2$ (5)	—	65 °C	3.5 h	10%
9	Br	MeCN	$PdCl_2(MeCN)_2$ (10)	—	70 °C	3 h	<24%[c]
10	Br	THF	$PdCl_2(MeCN)_2$ (5)	—	70 °C	3 h	<24%[c]
11	Br	THF	$PdCl_2(PPh_3)_2$ (5)	—	65 °C	3.5 h	<44%[c]
12	Br	DMSO	$PdCl_2(PPh_3)_2$ (5)	—	65 °C	3.5 h	<25%[c]
13	Br	PhMe	$PdCl_2(PPh_3)_2$ (5)	—	70 °C	3 h	<47%[c]
14	Br	CH_2Cl_2	$PdCl_2(PPh_3)_2$ (5)	—	60 °C	24 h	<48%[d]
15	*Br*	*Acetone*	*$PdCl_2(PPh_3)_2$ (5)*	—	*rt*	*20 h*	*48%*
16	Br	Acetone	$PdCl_2(PPh_3)_2$ (5)	—	60 °C	4 h	<45%
17	Cl	Acetone	$PdCl_2(PPh_3)_2$ (5)	—	rt	22 h	47%
18	I	Acetone	$PdCl_2(PPh_3)_2$ (5)	—	rt	20 h	73%
19	*I*	*Acetone*	*$PdCl_2(PPh_3)_2$ (5)*	—	*60 °C*	*4 h*	*83%*
20	I	Acetone	$AgNO_3$ (5)	—	rt	237 h	16%

[a] 0.018–0.06 M solution of substrate.
[b] In all cases was the starting material completely consumed.
[c] The product was not pure.
[d] In a closed pressure vessel.

of isatin (**2**) was obtained from **1** using $AgNO_3$ (5 mol %), but only after prolonged reaction times (16%, 437 h, ambient temperature entry 20).

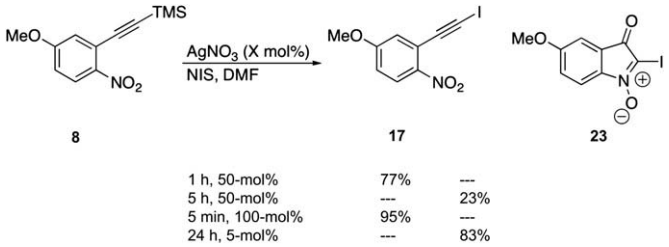
A selection of 2-nitro-1-[2-(trimethylsilyl)ethynyl]benzenes having both electron-donating and electron-withdrawing substituents was prepared using a Sonogashira coupling of 1-halo-2-nitrobenzenes with trimethylsilylethyne in 80–99% yield. The coupling reactions are summarized in Table 2 (entry 1–7). In addition a pyridine analogue (**13**) was also prepared (entry 8). The TMS-alkynes were subsequently transformed into iodo-alkynes using NIS in the presence of a catalytic amount of silver nitrate in *N*,*N*-dimethylformamide as the solvent.[9] It should be noted that the halo-alkyne intermediates **1**, **3**–**4**, and **14**–**22** are relatively unstable and decompose upon standing at ambient temperature.

Table 2
Sonogashira coupling→iodination→isatin formation

Entry[a]	Halobenzene	TMS-alkyne[b]	Iodo-alkyne[b]	Isatin[b]
				
1	R=4-NO_2	**5** (80%)	**14** (77%)	**25** (55%)
2	R=4-Cl	**6** (97%)	**15** (87%)	**26** (47%)
3	R=4-OMe	**7** (92%)	**16** (86%)	**27** (59%)
4	R=5-OMe	**8** (87%)	**17** (77%)	**28** (61%)
5	R=3-Me	**9** (99%)	**18** (99%)	**29** (70%)
6	R=4-Me	**10** (99%)	**19** (99%)	**30** (59%)
7	R=6-Me	**11** (89%)	**20** (93%)	**31** (52%)
				
8		**13** (66%)	**22** (61%)	**33** (0%)

[a] For experimental details see Experimental Section.
[b] Yield of isolated material after chromatography in parenthesis.

Most iodination reactions proceeded uneventfully and the expected iodo-alkyne products were obtained in good to excellent yields. However, reaction of the methoxy-substituted substrate **8** with NIS–$AgNO_3$ gave two different products depending on the catalyst loading and reaction time. At 50 mol % catalyst loading, reaction of **8** for 1 h at ambient temperature gave the expected iodo-alkyne **17**. In contrast, a prolonged reaction time (5 h) gave surprisingly an isatogen, 2-iodo-5-methoxy-3-oxo-3*H*-indole 1-oxide (**23**) (Scheme 2). Iodo-alkyne **17** was obtained in 95% yield after 5 min using a full equivalent of $AgNO_3$. The yield of the **23** (83%) was also improved by reaction of **8** with NIS in the presence of 5 mol % $AgNO_3$ for 24 h. The structure of **23** was confirmed by a single crystal X-ray analysis (Fig. 1). The formation of isatogens was not observed for any of the other TMS-alkynes examined. It should be noted that 2-halogenated isatogens have to our knowledge not been reported in the literature.



Scheme 2.

An unexpected formation of an isatin was observed upon treatment of TMS-alkyne **9** with NBS–$AgNO_3$ (Scheme 3). In the event, reaction of **9** with NBS in the presence of a catalytic amount of silver nitrate gave 5-bromo-7-methylisatin (**24**) in low isolated yield. The isatin formation was accompanied by bromination in the 5-position this reaction. Related brominations of isatins in the 5-position have been reported using NBS.[8,10] In a similar fashion, reaction of **9** with NIS–$AgNO_3$ gave 7-methylisatin (**31**) in low

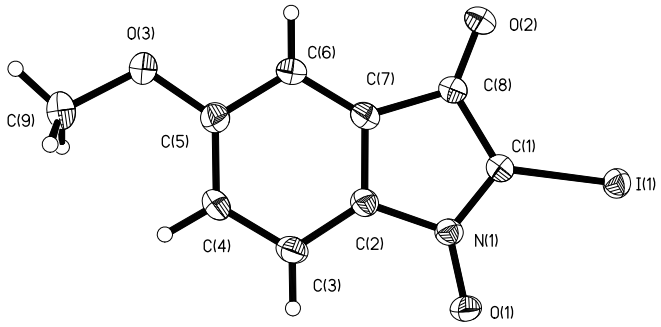
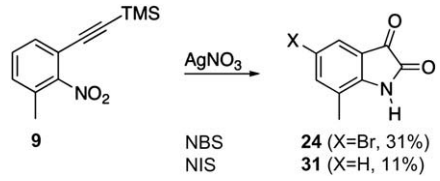


Figure 1. Perspective view of the molecular structure of **23** ($C_9H_6INO_3$) with the atom labeling scheme. The thermal ellipsoids are scaled to enclose 30% probability.

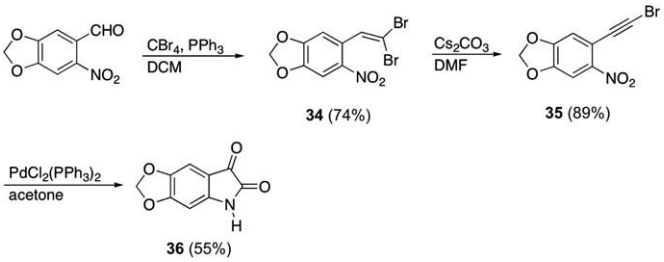


Scheme 3.

isolated yield. The last two examples and the reaction shown in Table 1 (entry 20) were the only examples that directly furnished isatins in the absence of a palladium catalyst.

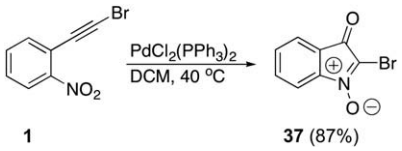
The iodoalkynes prepared were treated with $PdCl_2(PPh_3)_2$ (5 mol %) in acetone at ambient temperature immediately after chromatographic purification or as crude products. Isatins were obtained from all substituted 1-(2-iodoethynyl)-2-nitrobenzenes examined in 47–70% isolated yield (Table 2). Both electron-withdrawing (entry 1) and electron-donating groups (entries 3–4) were tolerated on the aromatic ring. Sterically more hindered substrates both adjacent to the iodoalkyne (entry 6) and the nitro group (entry 7) did not interfere with the reaction. Reaction of the pyridine derivative **22** resulted in complete disappearance of the starting material however, no identifiable product was isolated (entry 8).

As a final example of isatin formation, bromo-alkyne (**35**) was prepared from 6-nitrobenzo[1,3]dioxole-5-carboxaldehyde via a Corey–Fuchs reaction to give **34** followed by elimination of HBr using cesium carbonate. Reaction of **35** with $PdCl_2(PPh_3)_2$ in acetone gave the expected the isatin **36** in 55% yield (Scheme 4).



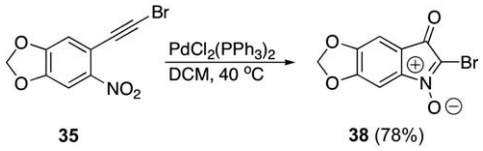
Scheme 4.

In all reactions forming isatins, for example in reaction of **1** to **2**, a rapid color change to orange followed by a more gradual change to red was observed. In an attempt to elucidate the structure of the orange intermediate, **1** was reacted in dichloromethane with $PdCl_2(PPh_3)_2$ (10 mol %) for 45 min. The solvent was removed and the crude product was rapidly purified by chromatography on silica gel to give an orange solid. NMR analysis of the product indicated the structure to be 2-bromoisatogen (**37**) (Scheme 5). In contrast to the previously discussed 5-methoxy-2-bromoisatogen (**23**) (Scheme 2), the latter compound was unstable at −20 °C and decomposed within a few days at ambient temperature to isatin.



Scheme 5.

The formation of an isatogen is not surprising considering the recently described palladium(II)-catalyzed syntheses of 2-arylisatogens and related derivatives from 1-(2-arylethynyl)-2-nitroarenes.[11–13] The parent isatogen was first prepared by Baeyer by reaction of 1-ethynyl-2-nitrobenzene[14] or 3-(2-nitrophenyl)-2-propynoic acid[15] with cold concentrated sulfuric acid. The latter synthesis probably involves decarboxylation to form 1-ethynyl-2-nitrobenzene followed by a cyclization reminiscent of the reaction seen in Scheme 5. More recently, direct oxidation of indoles using MoO_5–HMPA[16] or oxidation of 2,3-dihydroindoles with 3-chloroperbenzoic acid[17] to isatogens have been reported. Although the mechanism of the formation of isatins is not clear at the present time, the isatins discussed herein are most likely formed via the corresponding 2-halo-isatogens. A second example of a stable isatogen **38** was isolated from reaction of **35** in good isolated yield (Scheme 6).



Scheme 6.

Yamamoto et al. has developed a gold tribromide-catalyzed annulation of 2-(1-alkyn-1-yl)-1-nitrobenzenes to form isatogens.[18] It was of interest to examine if $AuBr_3$ would catalyze the formation of isatin from **1**. However, reaction of **1** with $AuBr_3$ in CH_2Cl_2 did not affect cyclization to **2**. The starting material was recovered unchanged after 5 days.

3. Summary

A regioselective novel palladium-catalyzed synthesis of isatins from 1-(2-haloethynyl)-2-nitrobenzenes have been developed. The isatins are formed via the corresponding, thermally labile, 2-halo-isatogens.

4. Experimental section

4.1. General procedures

All NMR spectra were determined in $CDCl_3$ at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR) unless otherwise noted. The chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^1H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. Results of APT (attached proton test)—^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (+) denotes CH_3 or CH and (−) denotes CH_2 or C.

Triethylamine, acetone–hexanes, acetonitrile, dichloromethane and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under an argon atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Melting points (uncorrected) were recorded directly from products

obtained by chromatography. Elemental Analyses were performed by Atlantic Microlab, Inc., Norcross, GA. High Resolution Mass Spectra (HRMS) were performed at University of California Riverside Mass Spectrometry Center and in the C. Eugene Bennett Department of Chemistry at West Virginia University.

Compounds **1**,[19] **2**,[20] **24**,[21] **26**,[20] **27**,[20] **28**,[22] **29**,[23] **30**,[20] **36**,[24] have previously been described and all spectral data (^{1}H NMR, ^{13}C NMR, IR) are in complete accordance with literature values. Compounds **4**,[25] **11** and **13**,[26] **25**,[8] **31**[27] have previously been described but without spectroscopical data. A number of compounds (**4**, **14**–**20**, **37**) noticeably decomposed at ambient temperature thus, combustion analysis or HRMS were not performed.

4.2. 2,4-Dinitro-1-[2-(trimethylsilyl)ethynyl]benzene (5)

To a solution of 2,4-dinitro-1-bromobenzene (500 mg, 2.01 mmol) in triethylamine (Et_3N, 15 mL) was added trimethylsilylethyne (217 mg, 2.21 mmol), CuI (28.7 mg, 0.151 mmol), and $PdCl_2(PPh_3)_2$ (70.5 mg, 0.101 mmol). The reaction mixture was stirred at ambient temperature under an argon atmosphere (24 h). The solvent was removed under reduced pressure and the crude product was purified by chromatography (hexanes/EtOAc, 9:1) to give **5** (425 mg, 1.61 mmol, 80%) as a yellow solid. Mp 65–68 °C; ^{1}H NMR δ 8.88 (d, J=2.3 Hz, 1H), 8.42 (dd, J=8.5, 2.4 Hz, 1H), 7.84 (d, J=8.7 Hz, 1H), 0.31 (s, 9H); ^{13}C NMR δ 149.9 (+), 146.4 (+), 136.2 (−), 124.2 (+), 120.1 (−), 111.3 (+), 97.6 (+), −0.72 (−); IR (neat) 3092, 2962, 1594 cm^{-1}; GC–MS (EI) m/z 264 (M^+), 249 (M^+−15, 100%). Anal. Calcd for $C_{11}H_{12}N_2O_4Si$: C, 49.99; H 4.58; N, 10.60. Found: C, 50.26; H 4.58; N, 10.38.

4.3. 4-Chloro-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (6)

Reaction of 4-chloro-2-nitro-1-iodobenzene (500 mg, 1.76 mmol), trimethylsilylethyne (191 mg, 1.94 mmol), CuI (25.0 mg, 0.136 mmol), and $PdCl_2(PPh_3)_2$ (62.0 mg, 0.088 mmol) in Et_3N (20 mL), as described for **5** (ambient temperature, 9 h) gave after workup and chromatography (hexanes/EtOAc, 95:5) **6** (430 mg, 1.70 mmol, 97%) as a yellow solid. Mp 39–41 °C; ^{1}H NMR δ 7.92 (d, J=2.0 Hz, 1H), 7.53 (d, J=8.3 Hz, 1H), 7.46 (dd, J=8.5, 2.0 Hz, 1H), 0.22 (s, 9H); ^{13}C NMR δ 150.2 (+), 135.8 (−), 134.5 (+), 132.8 (−), 124.6 (−), 116.7 (+), 105.0 (+), 98.2 (+), −0.57 (−); IR (neat) 3096, 2961, 2164 cm^{-1}; GC–MS (EI) m/z 253 (M^+), 238 (M^+−15), 73 ($SiMe_3^+$, 100%). Anal. Calcd for $C_{11}H_{12}ClNO_2Si$: C, 52.06; H 4.77; N, 5.52. Found: C, 52.37; H 4.86; N, 5.87.

4.4. 4-Methoxy-2-nitro-1-[2-(trimethylsilyl)ethynyl]-benzene (7)

Reaction of 4-methoxy-2-nitro-1-iodobenzene (500 mg, 1.79 mmol), trimethylsilylethyne (194 mg, 1.97 mmol), CuI (26.0 mg, 0.134 mmol), and $PdCl_2(PPh_3)_2$ (62.8 mg, 0.090 mmol) in Et_3N (20 mL), as described for **5** (ambient temperature, 22 h) gave after workup and chromatography (hexanes/EtOAc, 95:5), **7** (410 mg, 1.65 mmol, 92%) as a yellow solid. Mp 69–71 °C; ^{1}H NMR δ 7.49 (d, J=8.7 Hz, 1H), 7.43 (d, J=2.6 Hz, 1H), 7.46 (dd, J=8.7, 2.8 Hz, 1H), 3.83 (s, 3H), 0.22 (s, 9H); ^{13}C NMR δ 159.5 (+), 150.9 (+), 135.9 (−), 119.2 (−), 110.3 (+), 109.2 (−), 101.0 (+), 99.4 (+), 55.8 (−), −0.40 (−); IR (neat) 2161, 1620, 1530 cm^{-1}; GC–MS (EI) m/z 249 (M^+), 234 (M^+−15, 100%). Anal. Calcd for $C_{12}H_{15}NO_3Si$: C, 57.80; H 6.06; N, 5.62. Found: C, 58.39; H 6.55; N, 5.30; HRMS calcd for $C_{12}H_{16}NO_3Si$ ($M+H^+$) 250.0899, found 250.0894.

4.5. 2-(5-Methoxy-2-nitrophenyl)-1-trimethylsilylethyne (8)

Reaction of 5-methoxy-2-nitro-1-iodobenzene (1.00 g, 3.58 mmol), trimethylsilylethyne (387 mg, 3.97 mmol), CuI (51.0 mg, 0.269 mmol), and $PdCl_2(PPh_3)_2$ (126 mg, 0179 mmol) in Et_3N (20 mL), as described for **5** (ambient temperature, 24 h) gave after workup and chromatography (hexanes/EtOAc, 9:1), **8** (780 mg, 3.13 mmol, 87%) as a yellow solid. Mp 66–68 °C; ^{1}H NMR δ 7.95 (d, J=9.1 Hz, 1H), 6.96 (d, J=2.8 Hz, 1H), 6.82 (dd, J=9.1, 2.8 Hz, 1H), 3.81 (s, 3H), 0.24 (s, 9H); ^{13}C NMR δ 162.5 (+), 142.6 (+), 126.7 (−), 120.2 (+), 119.0 (−), 114.4 (−), 103.2 (+), 99.8 (+), 55.8 (−), 0.59 (−); IR (neat) 2966, 2898, 2165, 1602 cm^{-1}; GC–MS (EI) m/z 249 (M^+). Anal. Calcd for $C_{12}H_{15}NO_3Si$: C, 57.80; H 6.06; N, 5.62. Found: C, 57.97; H 6.31; N, 5.77.

4.6. 3-Methyl-2-nitro-1-[2-(trimethylsilyl)ethynyl]-benzene (9)

Reaction of 3-methyl-2-nitro-1-iodobenzene (500 mg, 1.90 mmol), trimethylsilylethyne (205 mg, 2.09 mmol), CuI (27.0 mg, 0.143 mmol), and $PdCl_2(PPh_3)_2$ (67.0 mg, 0.095 mmol) in Et_3N (20 mL), as described for **5** (ambient temperature, 20 h) gave after workup and chromatography (hexanes/EtOAc, 95:5), **9** (441 mg, 1.89 mmol, 99%) as a yellow solid. Mp 39–41 °C; ^{1}H NMR δ 7.40 (dd, J=7.5, 2.0 Hz, 1H), 7.31 (t, J=7.7 Hz, 1H), 7.24 (dd, J=7.5, 1.6 Hz, 1H), 2.33 (s, 3H), 0.24 (s, 9H); ^{13}C NMR δ 153.1 (+), 131.3 (−), 130.9 (−), 129.8 (+), 129.8 (−), 116.2 (+), 101.7 (+), 97.7 (+), 17.4 (−), −0.50 (−); IR (neat) 2962, 2160, 1600 cm^{-1}; GC–MS (EI) m/z 233 (M^+), 73 ($SiMe_3^+$, 100%). Anal. Calcd for $C_{12}H_{15}NO_2Si$: C, 61.77; H 6.48; N, 6.00. Found: C, 62.28; H 6.64; N, 6.30; HRMS calcd for $C_{12}H_{16}NO_2Si$ ($M+H^+$) 234.0950, found 234.0944.

4.7. 6-Methyl-2-nitro-1-[2-(trimethylsilyl)ethynyl]-benzene (11)

Reaction of 6-methyl-2-nitro-1-iodobenzene (1.30 g, 4.94 mmol), trimethylsilylethyne (0.77 mL, 5.41 mmol), CuI (70.5 mg, 0.370 mmol), and $PdCl_2(PPh_3)_2$ (173 mg, 0.246 mmol) in Et_3N (25 mL), as described for **5** (50 °C, 10 h) gave after workup and chromatography (hexanes), **11** (1.02 g, 4.38 mmol, 89%) as a faint yellow oil. ^{1}H NMR (600 MHz) δ 7.76 (d, J=8.4 Hz, 1H), 7.45 (d, J=7.2 Hz, 1H), 7.30 (t, J=8.1 Hz, 1H), 2.51 (s, 3H), 0.28 (s, 9H); ^{13}C NMR (150 MHz) δ 151.0, 143.7, 133.6, 127.9, 121.6, 117.6, 108.5, 97.6, 21.2, −0.34; IR (neat) 2960, 1528, 1346, 1249 cm^{-1}; HRMS calcd for $C_{12}H_{16}NO_2Si$ ($M+H^+$) 234.0950, found 234.0946.

4.8. 3-Nitro-1-[2-(trimethylsilyl)ethynyl]pyridine (13)

Reaction of 2-chloro-3-nitropyridine (750 mg, 4.73 mmol), trimethylsilylethyne (511 mg, 5.20 mmol), CuI (68.0 mg, 0.355 mmol), and $PdCl_2(PPh_3)_2$ (166 mg, 0.237 mmol) in Et_3N (15 mL), as described for **5** (ambient temperature, 48 h) gave after workup and chromatography (hexanes/EtOAc, 9:1), **13** (682 mg, 3.10 mmol, 66%) as a brown solid. Mp 36–38 °C; ^{1}H NMR δ 8.81 (dd, J=4.8, 1.6 Hz, 1H), 8.34 (dd, J=8.3, 1.6 Hz, 1H), 7.47 (dd, J=8.3, 4.7 Hz, 1H), 0.33 (s, 9H); ^{13}C NMR δ 153.2 (−), 147.2 (+), 136.6 (+), 132.2 (−), 123.0 (−), 105.1 (+), 98.7 (+), −0.33 (−); IR (neat) 2962, 2160, 1591, 1527 cm^{-1}; GC–MS (EI) m/z 220 (M^+), 73 ($SiMe_3^+$, 100%).

4.9. 2-Nitro-1-[2-bromoethynyl]benzene (1)

To a solution of 1-(2,2-dibromoethenyl)-2-nitrobenzene[28] (75 mg, 0.24 mmol) in DMF (3 mL) was added cesium carbonate (160 mg, 0.49 mmol) and the reaction mixture was stirred (ambient temp, 4 h). Dichloromethane (30 mL) was added, the organic phase was washed with water (3×30 mL), dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 9:1) affording **1** (52 mg, 0.24 mmol, 98%) as a yellow solid. Mp 98–100 °C (lit.[19] 94–95 °C).

4.10. 2-Nitro-1-[2-chloroethynyl]benzene (3)[29]

To a solution of 2-nitro-1-ethynylbenzene (612 mg, 4.16 mmol) in CCl_4 (10 mL) was added K_2CO_3 (690 mg, 4.99 mmol) and tetrabutylammonium fluoride (TBAF, 54.0 mg, 0.21 mmol). After stirring at ambient temperature (3 h), the solvent was removed under reduced pressure to give a grey solid. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **3** (646 mg, 3.56 mmol, 86%) as a pale yellow solid. Mp 83–85 °C; ^{1}H NMR δ 8.06 (d, J=8.1 Hz, 1H), 7.65 (dd, J=7.7, 1.6 Hz, 1H), 7.59 (td, J=7.3, 1.4 Hz, 1H), 7.47 (td, J=8.1, 1.8 Hz, 1H); ^{13}C NMR δ 149.8 (+), 135.2 (−), 132.9 (−), 129.0 (−), 124.6 (−), 117.4 (+), 76.0 (+), 64.8 (+); IR (neat) 2358, 2219 cm^{-1}. Anal. Calcd for $C_8H_4ClNO_2$: C, 52.92; H 2.22; N, 7.71. Found: C, 52.94; H 2.35; N, 7.53.

4.11. 2-Nitro-1-[2-iodoethynyl]benzene (4)

To a solution of **5**[30] (500 mg, 2.28 mmol) in anhydrous DMF (10 mL) was added $AgNO_3$ (19.4 mg, 0.114 mmol). The reaction vessel was wrapped in aluminum foil and was cooled to 0 °C. *N*-Iodosuccinimide (NIS, 564 mg, 2.51 mmol) was added and the reaction mixture was allowed to warm to ambient temperature under an argon atmosphere (3 h). The reaction mixture was cooled to 0 °C. Ice-cold water (20 mL) was added and the mixture was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with water (3×20 mL), dried ($MgSO_4$), filtered, and the solvents were removed at reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 9:1) to give **4** (535 mg, 1.96 mmol, 86%) as a yellow solid. Mp 68–70 °C; ^{1}H NMR δ 8.07 (dd, J=8.1, 1.0 Hz, 1H), 7.66 (dd, J=7.3, 1.4 Hz, 1H), 7.58 (td, J=7.1, 1.2 Hz, 1H), 7.47 (td, J=7.3, 1.8 Hz, 1H); ^{13}C NMR δ 150.2 (+), 135.8 (−), 132.8 (−), 129.1 (−), 124.6 (−), 118.5 (+), 89.0 (+), 16.9 (+); IR (neat) 2455, 2152 cm^{-1}.

4.12. 2,4-Dinitro-1-[2-iodoethynyl]benzene (14)

Reaction of **5** (50.0 mg, 0.189 mmol), $AgNO_3$ (1.60 mg, 0.0095 mmol), and NIS (46.8 mg, 0.208 mmol) in DMF (3 mL), as described for **4** (3 h), gave after workup and chromatography (hexanes/EtOAc, 9:1) **14** (46.2 mg, 0.208 mmol, 77%) as a yellow solid. Mp 115–117 °C; ^{1}H NMR δ 8.91 (d, J=2.4 Hz, 1H), 8.44 (dd, J=8.5, 2.4 Hz, 1H), 7.86 (d, J=8.7 Hz, 1H); ^{13}C NMR δ 150.3 (+), 146.6 (+), 137.1 (−), 126.9 (−), 124.3 (+), 120.3 (−), 88.0 (+), 25.9 (+); IR (ATR) 3094, 2161, 1592 cm^{-1}.

4.13. 4-Chloro-2-nitro-1-[2-iodoethynyl]benzene (15)

Reaction of **6** (360 mg, 1.42 mmol), $AgNO_3$ (24.1 mg, 0.142 mmol), and NIS (352 mg, 1.56 mmol) in DMF (10 mL), as described for **4** (3 h), gave after workup and chromatography (hexanes/EtOAc, 9:1) **15** (379 mg, 1.23 mmol, 87%) as a yellow solid. Mp 92–94 °C; ^{1}H NMR δ 8.04 (d, J=1.6 Hz, 1H), 7.59 (d, J=8.9 Hz, 1H), 7.55 (dd, J=8.3, 1.8 Hz, 1H); ^{13}C NMR δ 150.4 (+), 136.6 (−), 135.0 (+), 133.0 (−), 124.8 (−), 116.9 (+), 88.0 (+), 18.7 (+); IR 2165, 1555 cm^{-1}.

4.14. 4-Methoxy-2-nitro-1-[2-iodoethynyl]benzene (16)

Reaction of **7** (378 mg, 1.51 mmol), $AgNO_3$ (12.9 mg, 0.0757 mmol), and NIS (375 mg, 1.67 mmol) in DMF (10 mL), as described for **4** (1 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **16** (393 mg, 1.30 mmol, 86%) as a yellow solid. Mp 89–90 °C; ^{1}H NMR δ 7.53 (d, J=8.5 Hz, 1H), 7.52 (d, J=2.6 Hz, 1H), 7.10 (dd, J=8.7, 2.6 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR δ 159.7 (+), 151.2 (+), 136.6 (−), 119.5 (−), 110.6 (+), 109.3 (−), 88.8 (+), 56.0 (−), 13.6 (+); IR (neat) 2170, 1560, 1527 cm^{-1}.

4.15. 5-Methoxy-2-nitro-1-[2-iodoethynyl]benzene (17)

Reaction of **8** (300 mg, 1.276 mmol), $AgNO_3$ (122 mg, 0.658 mmol), and NIS (318 mg, 1.409 mmol) in DMF (2 mL), as described for **4** (1 h, rt), gave after workup and chromatography (hexanes/EtOAc, 8:2) **17** (299 mg, 0.987 mmol, 77%) as a yellow solid. Mp 87–88 °C; ^{1}H NMR δ 8.09 (d, J=9.1 Hz, 1H), 7.06 (d, J=2.7 Hz, 1H), 6.93 (dd, J=9.3, 2.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR δ 162.8 (+), 143.3 (+), 127.1 (−), 120.8 (+), 119.9 (+), 115.1 (+), 89.5 (+), 56.1 (−), 16.8 (+); IR (neat) 2160, 1606, 1573 cm^{-1}.

4.16. 3-Methyl-2-nitro-1-[2-iodoethynyl]benzene (18)

Reaction of **9** (175.0 mg, 0.751 mmol), $AgNO_3$ (135 mg, 0.771 mmol), and NIS (189 mg, 0.838 mmol) in DMF (5 mL), as described for **4** (20 min) at 0 °C, gave after workup **18** (200 mg, 0.697 mmol, 93%) as a yellow solid. The product decomposes upon standing at ambient temperature and on attempted purification on silica gel. ^{1}H NMR δ 7.55 (dd, J=7.5, 1.8 Hz, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.40 (dd, J=7.7, 1.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR δ 153.3 (+), 131.7 (−), 131.7 (−), 130.2 (+), 129.9 (−), 116.5 (+), 87.4 (+), 17.5 (−), 14.8 (+); IR (neat) 2928, 2169 cm^{-1}.

4.17. 4-Methyl-2-nitro-1-[2-iodoethynyl]benzene (19)

Reaction of 4-methyl-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (**10**)[31] (715 mg, 3.07 mmol), $AgNO_3$ (58 mg, 0.108 mmol), and NIS (768 mg, 3.40 mmol) in DMF (7 mL), as described for **4** (20 min) at 0 °C, gave after workup and chromatography (hexanes/EtOAc, 9:1) **19** (646 mg, 2.25 mmol, 73%) as a yellow solid. Mp 94–96 °C; ^{1}H NMR (600 MHz) δ 7.85 (s, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.37 (d, J=8.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (150 MHz) δ 150.5, 140.4, 135.8, 133.8, 125.1, 115.9, 89.2, 21.5, 15.2.

4.18. 6-Methyl-2-nitro-1-[2-iodoethynyl]benzene (20)

Reaction of **11** (135 mg, 0.579 mmol), $AgNO_3$ (53.0 mg, 0.303 mmol), and NIS (144 mg, 0.638 mmol) in DMF (4 mL), as described for **4** (5.5 h, 0 °C to rt), gave after workup and chromatography (hexanes/EtOAc, 9:1) **20** (155 mg, 0.54 mmol, 93%) as a yellow solid. Mp 87–88 °C; ^{1}H NMR (600 MHz) δ 7.81 (d, J=8.4 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.33 (t, J=8.1 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (150 MHz) δ 151.6, 144.9, 134.0, 128.4, 122.1, 118.1, 87.8, 21.3, 20.5; IR (neat) 2928, 2169 cm^{-1}.

4.19. 2-(3-Nitropyridyl)-1-iodoethyne (21)

Reaction of **13** (150 mg, 0.750 mmol), $AgNO_3$ (6.4 mg, 0.0375 mmol), and NIS (186 mg, 0.825 mmol) in DMF (15 mL), as described for **4** (1 h), gave after workup **21** (125 mg, 0.458 mmol, 61%) as a yellow solid. Mp 156–158 °C; ^{1}H NMR δ 8.81 (dd, J=4.8, 1.6 Hz, 1H), 8.37 (dd, J=8.3, 1.6 Hz, 1H), 7.55 (dd, J=8.3, 4.7 Hz, 1H); ^{13}C NMR δ 153.4 (+), 147.5 (−), 136.7 (−), 132.4 (+), 123.3 (+), 89.8 (−), 21.1 (−); IR (neat) 1593, 1520, 1339, 819, 759 cm^{-1}. Anal. Calcd for $C_7H_3IN_2O_2$: C, 30.68; H 1.10; N, 10.22. Found: C, 30.93; H 1.24; N, 9.73. HRMS (ESI) calcd for $C_7H_4IN_2O_2$ ($M+H^+$) 274.9318, found 274.9311.

4.20. 5-(2,2-Dibromoethen-1-yl)-6-nitrobenzo[1,3]dioxole (34)

To solution of carbon tetrabromide (3.40 g, 10.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added triphenylphosphine (5.37 g, 20.5 mmol) in three portions in 10 min intervals. 6-Nitrobenzo[1,3]dioxole-5-carboxaldehyde (1.00 g, 5.13 mmol) was added and the resulting mixture was allowed to warm to ambient temperature. After 16 h, the solvent was removed at reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc,

7:3) to give **34** (1.20 g, 3.76 mmol, 74%) as a yellow solid. Mp 162–164 °C; ^{1}H NMR (600 MHz) δ 7.71 (s, 1H), 6.95 (s, 1H), 6.17 (s, 2H); ^{13}C NMR (150 MHz) δ 151.9, 148.2, 141.2, 134.4, 128.0, 110.1, 105.5, 103.3, 92.6; IR (neat) 1503, 1483, 1318, 1028, 830 cm^{-1}; HRMS calcd for $C_9H_6Br_2NO_4$ ($M+H^+$) 349.8664, found 349.8658

4.21. 5-(2-Bromoethyn-1-yl)-6-nitrobenzo[1,3]dioxole (35)

A solution of **34** (500 mg, 1.57 mmol) and Cs_2CO_3 (1.02 g, 3.14 mmol) in DMF (10 mL) was stirred under an argon atmosphere at 70 °C (5 h). Dichloromethane (50 mL) was added and the resulting mixture was washed with water (2×50 mL), dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure. The crude yellow product was purified by chromatography (hexanes/EtOAc, 7:3) to give **35** (331 mg, 1.39 mmol, 89%) as a yellow solid. Mp 104–106 °C; ^{1}H NMR δ 7.55 (s, 1H), 6.98 (s, 1H), 6.15 (s, 2H); ^{13}C NMR δ 151.5 (+), 148.2 (+), 145.2 (+), 114.0 (+), 113.2 (−), 105.4 (−), 103.4 (+), 75.7 (+), 57.7 (+); IR (neat) 1603 cm^{-1}; GC–MS (EI) *m*/*z* 272 (M^++2), 270 (M^+), 163 (100%). Anal. Calcd for $C_9H_4BrNO_4$: C, 40.03; H 1.49; N, 5.19. Found: C, 40.09; H 1.61; N, 4.93.

4.22. 1*H*-Indole-2,3-dione (2)

To a solution of **4** (50.0 mg, 0.183 mmol) in acetone (10 mol) was added, under an argon atmosphere, bis(triphenylphosphine)palladium dichloride ($PdCl_2(PPh_3)_2$, 6.4 mg, 0.009 mmol) and the resulting mixture was stirred at 60 °C (4 h). The solvent was removed under reduced pressure and the residue was purified by chromatography (hexanes/EtOAc, 7:3) to afford **2** (22.3 mg, 0.152 mmol, 83%) as a red solid. Mp 192–194 °C (lit. Mp 193–195 °C).

Reaction of **1** (100 mg, 0.42 mmol) with $PdCl_2(PPh_3)_2$ (15.5 mg, 0.022 mmol) in acetone (10 mL), as described above (ambient temp, 20 h), gave after chromatography (hexanes/EtOAc, 7:3) **2** (31 mg, 0.21 mmol, 48%) as a red solid.

Reaction of **3** (50 mg, 0.28 mmol) with $PdCl_2(PPh_3)_2$ (9.7 mg, 0.014 mmol) in acetone (10 mL), as described above (ambient temp 22 h), gave after chromatography (hexanes/EtOAc, 7:3) **2** (19 mg, 0.13 mmol, 47%) as a red solid.

4.23. 5-Bromo-7-methylindole-2,3-dione (24)

Reaction of **9** (400 mg, 1.71 mmol) with $AgNO_3$ (14.6 mg, 0.086 mmol), and NBS (336 mg, 1.89 mmol) in DMF (10 mL), as described for **4** (ambient temp, 45 h), gave after workup and chromatography (hexanes/EtOAc, 7:3) **24** (129 mg, 0.54 mmol, 31%) as a red solid. Mp 246–249 °C (lit.[32] mp 240 °C).

4.24. 6-Nitroindole-2,3-dione (25)

Reaction of **14** (140 mg, 0.44 mmol) with $PdCl_2(PPh_3)_2$ (16 mg, 0.023 mmol) in acetone (6 mL), as described for **2** (ambient temp, 6 h), gave after chromatography (hexanes/EtOAc, 6:4) **25** (40 mg, 0.208 mmol, 47%) as a yellow solid. Mp (decomp.) 268 °C (lit.[33] 281–284 °C); IR (ATR) 1747, 1715, 1327 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.35 (br s, 1H), 7.86 (dd, *J*=8.4, 1.8 Hz, 1H), 7.75 (d, *J*=7.8 Hz, 1H), 7.54 (d, *J*=1.8 Hz, 1H); ^{13}C NMR (150 MHz) δ 183.1, 158.8, 152.5, 150.7, 125.4, 122.4, 117.7, 106.3.

4.25. 6-Chloroindole-2,3-dione (26)

Reaction of **15** (50 mg, 0.16 mmol) with $PdCl_2(PPh_3)_2$ (15 mg, 0.021 mmol) in acetone (10 mL), as described for **2** (ambient temp, 96 h), gave after chromatography (hexanes/EtOAc, 7:3) **26** (12 mg, 0.076 mmol, 47%) as a yellow solid. Mp 255 °C (lit.[34] 261–262 °C).

4.26. 6-Methoxyindole-2,3-dione (27)

Reaction of **16** (90.0 mg, 0.297 mmol) with $PdCl_2(PPh_3)_2$ (12.0 mg, 0.017 mmol) in acetone (10 mL), as described for **2** (ambient temp, 48 h), gave after chromatography (hexanes/EtOAc, 1:1) **27** (31.0 mg, 0.175 mmol, 59%) as a yellow solid. Mp (dec) 220 °C (lit.[35] 229–230 °C).

4.27. 5-Methoxyindole-2,3-dione (28)

Reaction of **17** (290 mg, 0.957 mmol) with $PdCl_2(PPh_3)_2$ (35 mg, 0.049 mmol) in acetone (10 mL), as described for **2** (ambient temp, 36 h), gave after chromatography (hexanes/EtOAc, 6:4) **28** (103 mg, 0.581 mmol, 61%) as a dark red solid. Mp 190–195 °C (lit.[35] mp 200–201 °C).

4.28. 7-Methylindole-2,3-dione (29)

Reaction of **18** (170 mg, 0.592 mmol) with $PdCl_2(PPh_3)_2$ (22 mg, 0.031 mmol) in acetone (10 mL), as described for **2** (ambient temp, 30 h), gave after chromatography (hexanes/EtOAc, 6:4) **29** (67 mg, 0.416 mmol, 70%) as an orange solid. Mp 265–268 °C (lit.[22a] 267–269 °C).

4.29. 6-Methylindole-2,3-dione (30)

Reaction of **19** (165 mg, 0.575 mmol) with $PdCl_2(PPh_3)_2$ (22 mg, 0.031 mmol) in acetone (10 mL), as described for **2** (ambient temp, 1 h), gave after chromatography (hexanes/EtOAc, 6:4) **30** (55 mg, 0.342 mmol, 59%) as an orange solid. Mp 182–184 °C (lit.[36] 187 °C).

4.30. 4-Methylindole-2,3-dione (31)

Reaction of **20** (120 mg, 0.42 mmol) with $PdCl_2(PPh_3)_2$ (2.3 mg, 0.0032 mmol) in acetone (10 mL), as described for **2** (ambient temp, 1 h), gave after chromatography (hexanes/EtOAc, 7:3) **31** (32 mg, 0.22 mmol, 52%) as red solid. Mp 182–184 °C (lit.[37] 184–185 °C); ^{1}H NMR (600 MHz) δ 8.13 (br s, 1H), 7.40 (t, *J*=7.8 Hz, 1H), 6.89 (d, *J*=7.2 Hz, 1H), 6.71 (d, *J*=7.8 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (150 MHz) δ 183.5, 159.3, 149.2, 141.9, 138.1, 126.4, 116.6, 109.6, 18.3; IR (ATR) 1722, 1710, 1603 cm^{-1}.

4.31. 5*H*-[1,3]Dioxolo[4,5-*f*]indole-6,7-dione (36)

Reaction of **35** (15.3 mg, 0.064 mmol) with $PdCl_2(PPh_3)_2$ (2.3 mg, 0.0032 mmol) in acetone (4 mL), as described for **2** (ambient temp, 18 h), gave after chromatography (hexanes/EtOAc, 6:4) **36** (6.8 mg, 0.0353 mmol, 55%) as a red solid. Mp 280 °C (lit.[38] mp 284 °C).

4.32. 2-Bromo-3-oxo-3*H*-indole 1-oxide (37)

To a solution of **1** (200 mg, 0.885 mmol) in CH_2Cl_2 (15 mL) was added $PdCl_2(PPh_3)_2$ (62.1 mg, 0.0885 mmol). The reaction mixture was heated at reflux for 45 min. The solvent was removed under reduced pressure to give an orange solid that was purified by chromatography (hexanes/EtOAc, 6:4) to afford **37** (174 mg, 0.771 mmol, 87%) as an orange solid. ^{1}H NMR δ 7.74–7.55 (m, 4H); ^{13}C NMR δ 180.5, 147.8, 135.1, 135.0, 131.6, 131.5, 123.0, 122.3, 114.0; IR (ATR) 1735, 1652, 1506 cm^{-1}.

4.33. 2-Iodo-5-methoxy-3-oxo-3*H*-indole 1-oxide (23)

Reaction of **8** (122 mg, 0.401 mmol), $AgNO_3$ (20.1 mg, 0.0201 mmol), and NIS (99.0 mg, 0.441 mmol) in DMF (7 mL) as described for **4** (rt, 24 h) gave after workup and chromatography (hexanes/EtOAc, 8:2) **23** (99.6 mg, 0.329 mmol, 82%) as a red solid.

Mp 172–175 °C; ^{1}H NMR δ 7.55 (d, J=8.5 Hz, 1H), 7.16 (d, J=2.6 Hz, 1H), 7.01 (dd, J=8.5, 2.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR δ 182.9 (+), 162.3 (+), 141.9 (+), 125.8 (+), 117.6 (−), 115.3 (−), 108.9 (−), 95.2, (+), 56.3 (−); IR (ATR) 2359, 1706 cm^{-1}; HRMS (ESI) calcd for $C_9H_7INO_3$ (M+H$^+$) 303.9471, found 303.9468.

4.34. 6-Bromo-7-oxo-7*H*-[1,3]dioxolo[4,5-*f*]indole 5-oxide (38)

To a solution of **35** (500 mg, 1.85 mmol) in CH_2Cl_2 (20 mL) was added $PdCl_2(PPh_3)_2$ (65 mg, 0.093 mmol). The reaction mixture was heated at reflux for 10 min. The solvent was removed under reduced pressure and the resulting residue was purified by chromatography (hexanes/EtOAc, 8:2) to afford **38** (394 mg, 1.46 mmol, 79%) as a brown solid. Mp 125 °C (dec); ^{1}H NMR δ 7.17 (s, 1H), 7.05 (s, 1H) 6.17 (s, 2H); ^{13}C NMR (150 MHz) δ 179.7, 153.1, 150.1, 144.7, 117.4, 117.1, 103.6, 103.3, 97.8; IR (ATR) 1719, 1500, 1292, 1031 cm^{-1}; HRMS (ESI) calcd for $C_9H_5BrNO_4$ (M+H$^+$) 269.9402, found 269.9399.

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Supplementary data

CCDC-722562 (compound **23**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at http://www.ccdc.cam.c.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; email: deposit@ccdc.cam.sc.uk]. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.098.

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