Preparation of Dibenzo[e,g]isoindol-1-ones via Scholl-Type Oxidative Cyclization Reactions

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Supporting Information

ABSTRACT: A flexible synthesis of dibenzo[e,g]isoindol-1-ones has been developed. Dibenzo[e,g]isoindol-1-ones represent simplified benzenoid analogues of biological indolo[2,3-a]-pyrrolo[3,4-c]carbazol-5-ones (indolocarbazoles), compounds that have demonstrated a wide range of biological activity. The synthesis of the title compounds involved tetramic acid sulfonates. Different aryl groups were introduced at C4 of the heterocyclic ring via Suzuki–Miyaura cross-coupling reactions. Finally, mild Scholl-type oxidative cyclizations mediated by phenyliodine(III) bis(trifluoroacetate) (PIFA) converted some of the latter compounds into the corresponding dibenzo[e,g]-isoindol-1-ones. A systematic study of the oxidative cyclization revealed the following reactivity trend: 3,4-dimethoxyphenyl ≫ 3-methoxyphenyl > 3,4,5-trimethoxyphenyl > 4-methoxyphenyl ≈ phenyl. Overall, the oxidative cyclization required at least two methoxy groups distributed in the aromatic rings, at least one of which had to be located para to the site of the cyclization.

INTRODUCTION

Polycyclic-fused isoindol-1-ones have demonstrated promising utility as heterocyclic scaffolds in the search for enzyme inhibitors (Figure 1). A prominent member of this structural class is the natural product staurosporinone (1), a submicromolar inhibitor of protein kinase C (PKC) first isolated in 1986.2,3 The impressive biological activity inspired several total syntheses of 1, and the investigation into analogues that retain the indolo[2,3-a]pyrrolo[3,4-c]carbazol-5-one (indolocarbazole) backbone of 1. For example, the indolocarbazole analogue Go6976 (2) is a selective PKC inhibitor4 and HIV-1 antagonist.5 Several heterocyclic fused isoindol-1-ones,6 ring-modified analogues of 1, have also been prepared and their biological activity evaluated (e.g., 3,9 4,10 and 5,11). The synthesis of benzo[a]pyrrolo[3,4-c]carbazole-1-ones (e.g., 6) was also reported in 2008.12 Interestingly, only a small number of reports in the literature have described the preparation of the simpler ring system, dibenzo[e,g]isoindol-1-one 7,13 and none of these reports included an example of 7 that is N-unsubstituted. Dibenzo[e,g]isoindolones, in which both indole rings have been replaced with simple benzene rings, are potentially a new class of indolocarbazole analogues. Given our interest in the chemistry of 3,4-diaryl-3-pyrrolin-2-ones, along with the diverse biological activity associated with polycyclic-fused isoindol-1-ones, we decided to investigate the conversion of B into A (Scheme 1) via an intramolecular Scholl-type oxidative cyclization.15 In contrast, most known literature methods to A involve reduction of the corresponding maleimides C;4,6e this reduction often proves to be unselective in cases of nonsymmetrical substrates.16 There are several possible methods available for completing oxidative cyclizations to phenanthrenes and fused phenanthrenes; these methods include oxidative photocyclization,17 transition metal-mediated oxidative cyclization,18−21 and oxidative cyclization using nonmetal reagents.22−25 We chose to focus our attention on the latter given the mildness of the reagents and ease of use. Kita pioneered an array of different oxidative transformations.

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involving electron-rich arenes that used the hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA).26 PIFA-mediated cyclizations leading to phenanthrenes and fused phenanthrenes were subsequently reported by Domínguez24 and others.25 By exploring the PIFA-mediated oxidative cyclization of 3,4-diaryl-3-pyrrolin-2-ones, we set out to synthesize new dibeno[e,g]isoindol-1-one analogues of indolocarbazoles and related biologically active heterocyclic scaffolds including congeners containing either symmetrical or unsymmetrical substitution patterns in the phenanthrene rings or heterocyclic variants.

Our synthetic plan involved extending our synthesis of 3,4-diaryl-3-pyrrolin-2-ones from 3-aryltetramic acid triﬂates (Scheme 2).14b,c Our strategy allows for easy access to 3-

**Scheme 2. Synthetic Plan to Dibenzo[e,g]isoindol-1-ones**

pyrrolin-2-ones with different aryl groups at the 3- and 4-positions. The choice of arylacetic acid starting material leads to different aryl groups at the 3-positions (in blue), while different aryl groups can be introduced at the 4-position (in red) via Suzuki–Miyaura cross-coupling reactions with commercially available arylboronic acids. With a small library of 3,4-diaryl-3-pyrrolin-2-ones in hand, we explored their subsequent intramolecular Scholl-type oxidative cyclizations into dibenzo[e,g]isoindol-1-ones.

**RESULTS AND DISCUSSION**

We prepared methoxyl-substituted tetramic acids by extending our previously reported synthetic strategy to a 3-phenyltetramic acid (Table 1).14c Freshly prepared ethyl glycinate free amine was coupled with arylacetic acids in the presence of DCC/DMAP giving amidoesters 8 as white powders after trituration. Next, treatment of 8 with Boc₂O/DMAP gave the Boc-protected aceticamides 9.26 We next attempted to form the tetramic acids 10 by treatment of 9 with sodium tert-butoxide as we had done previously (9: Ar₃ = Ph).14b Unexpectedly, the attempted cyclocondensations of methoxyl-substituted acetamides 9 (b Ar₃ = 4'-methoxyphenyl; c Ar₃ = 3'-methoxyphenyl; d Ar₃ = 3',4'-dimethoxyphenyl) with sodium tert-butoxide failed to produce the corresponding tetracids 10. Fortunately, the use of potassium tert-butoxide gave methoxyl-substituted tetramic acids 10 in moderate yields. Treatment of 10 with triflic anhydride led to the corresponding triﬂates 11; in some of the runs, puriﬁcation of 11 led to the loss of the Boc protecting group and the formation of unprotected lactams 12.30 Triflates 12 were also obtained by treatment of puriﬁed 11 with PIFA in CH₂Cl₂ (the yields of these reactions leading to 12 are reported in Table 1). We subsequently found substrates 11c/12c to be capricious in the subsequent cross-coupling reactions, so we prepared the alternate cross-coupling substrate, tosylate 13c, by treatment of 10c with tosyl chloride and triethylamine.31

We briefly investigated an alternative synthesis of 12 that avoided the use of the Boc protecting group altogether. Cyclization of unprotected acetamides 8 with potassium tert-butoxide gave the corresponding N-unsubstituted 3-aryltetramic acids in isolated yields that were very low (<10%); we believe the low yields observed were due to the difﬁculty in purifying these unprotected tetracids and this strategy was not pursued further.32

We next examined Suzuki–Miyaura cross-coupling reactions of tetramic acid sulfonylates 11–13. Cross-coupling reactions of all three types of substrates with methoxyl-substituted arylboronic acids gave the corresponding 3,4-diaryl-3-pyrrolin-2-ones 14 and 15, respectively, in good to excellent yields in many cases (Table 2). As expected, we did observe higher yields using protected triﬂates 11 compared to unprotected triﬂates 12 (e.g., entry 5 vs entry 16), but we favored the use of unprotected triﬂates as it saves one synthetic operation per substrate. Inexplicably, cross-coupling reactions of either triﬂate 11c, unprotected triﬂate 12c, or tosylate 13c (substrates with a 3-methoxyphenyl group) suffered from low yields or gave intractable mixtures. Nonetheless, this strategy still allowed for the preparation of a small library of methoxyl-substituted 3,4-diaryl-3-pyrrolin-2-ones for our oxidative cyclization study.

We chose to start exploring intramolecular Scholl-type oxidative cyclizations of bis(3,4'-dimethoxyphenyl)-3-pyrrolin-2-ones 14dd and 15dd (Scheme 3) using PIFA.24–26 Satisfyingly, on our ﬁrst attempt, treatment of 14dd with PIFA and BF₃·Et₂O at −40 °C for 30 min led to the formation of dibenzo[e,g]isoindol-1-one 16dd in 55% yield. The reaction proceeded with loss of the Boc protecting group. We next tried the cyclization with N-unprotected lactam substrate 15dd and obtained 16dd in 93% yield. Since the yield was excellent for the free lactam, we subsequently used N-unprotected 3-pyrrolin-2-ones in all of the subsequent oxidative cyclization reactions. Evidence for the cyclization could readily be seen in the 1H NMR, which showed a signiﬁcant downﬁeld shift of the arene protons (δ6.8–7.0 in 15dd to 8.7–8.9 in 16dd) and methylene protons (δ4.32 in 15dd to δ4.67 in 16dd). We used this type of analysis to diagnose crude reaction mixtures involving the oxidative cyclizations.

A brief exploration of the reaction conditions of the oxidative cyclization with 15dd was conducted (Table 3). Extending the reaction time (entry 1 vs entry 2) slightly increased the yield (93 to 96%). The yield decreased slightly (96 to 90%) when the reaction was run at ±4 °C compared to ±40 °C (entry 2 vs
entry 3). Although the yields in entries 1–3 are effectively the same given the scale of these reactions (0.20–1.00 mmol), we chose the 4-h reaction time to make further comparisons. The use of either DDQ \(^2\) (entry 6) or m-CPBA \(^2\) (entry 7) as the oxidant and TFA as the acid led to the incomplete conversion of the starting material after 4 h at room temperature. The oxidative cyclization requires an oxidant as reactions run with just BF\(_3\)Et\(_2\)O (entry 5) or TFA (entry 8) and no oxidant led to the recovery of only starting material. Interestingly, a reaction run with just PIFA and no BF\(_3\)Et\(_2\)O led to the cyclized product in 75% yield (entry 4). Kita and co-workers observed a much greater conversion (91% with PIFA, BF\(_3\)Et\(_2\)O vs 25% with PIFA) in a similar comparative study of oxidative cyclization reactions leading to a dibenzo[a,e]-cycloheptene. \(^{26b}\)

We next examined the effect that methoxy-substitution had on the Scholl-type oxidative cyclization by comparing 15 different 3,4-diaryl-3-pyrrolin-2-one substrates 15 (Table 4). The substrates in vertical columns differ by the C3-aryl group (4-methoxyphenyl; 3-methoxyphenyl; 3,4-dimethoxyphenyl) and the substrates in horizontal rows differ by the C4-aryl group (phenyl; 4-methoxyphenyl; 3-methoxyphenyl; 3,4-dimethoxyphenyl; 3,4,5-trimethoxyphenyl). All of the oxidative cyclization reactions were run at −40 °C (acetoniitrile/CO\(_2\) bath) for 4 h, and then the solvent was removed, and the resulting crude reaction mixtures were analyzed by \(^1H\) NMR. It was convenient to estimate the conversion of starting material 15 to product 16 by examining the relative integrations (rounded to the nearest 10%) of the respective methylene protons (∼δ4.3 in 15 vs ∼δ4.7 in 16). All substrates containing one 3,4-dimethoxyphenyl group gave conversions between 60 and 90%, whereas the substrate containing two 3,4-dimethoxyphenyl groups (15dd) gave complete conversion. Substrates lacking a 3,4-dimethoxyphenyl group led to conversions under 50% with the exception of the substrate containing two 3-methoxyphenyl groups which gave 70% conversion. Finally, substrates containing just one methoxy group or no methoxy groups located para to the site of cyclization gave 0% conversion (16cb also gave 0% conversion). The following relative reactivity trend can be deduced from this data: 3,4-dimethoxyphenyl ≫ 3-methoxyphenyl > 3,4,5-trimethoxyphenyl > 4-methoxyphenyl ≈ phenyl. In addition, we did not observe any regioisomeric cyclization products in cases where more than one regioisomer was possible (although we can definitively rule out their existence).

We attempted to purify the crude reaction mixtures that contained greater than 50% conversion. Pure samples of dibenz[\(e,g\)]isoindol-1-ones 16, as demonstrated by \(^1H\) and \(^13C\) NMR, could be obtained by trituration of the crude reaction mixtures with ethanol. This process worked in the cases where yields are given in Table 4. Although our methodology is limited in scope to electron-rich substrates at this point, we were able to obtain seven analytically pure dibenz[\(e,g\)]-
isoindol-1-ones from these experiments, which demonstrates its potential for exploring this novel heterocyclic scaffold.

**CONCLUSION**

We have developed a flexible synthesis of 3,4-diaryl-3-pyrrolin-2-ones from 3-aryltetramic acids, which allowed for the preparation of a small library of methoxyphenyl-substituted analogues (symmetrical and unsymmetrical). This library of compounds was subjected to PIFA-mediated oxidative cyclization reactions leading to the corresponding dibenzo[e,g]isoindol-1-ones (phenanthrene-fused 3-pyrrolin-2-ones). The oxidative cyclization reaction worked better with substrates containing 3,4-dimethoxyphenyl groups and 3-methoxyphenyl groups compared to substrates containing 4-methoxyphenyl groups. This work should allow for further exploration into the synthesis of simplified analogues of indolocarbazoles including the further exploration of the biological activity of this class of molecules.

**EXPERIMENTAL SECTION**

**General Methods.** All reactions were performed under a positive argon atmosphere with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and dichloromethane (CH₂Cl₂) were purified by passage through a column of alumina utilizing a PureSolv 400 solvent purification system. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. ¹H NMR and ¹³C NMR chemical shifts are reported in parts per million (δ) using the solvent’s residual proton or carbon signal (CDCl₃: δH 7.26 ppm, δC 77.3 ppm; DMSO-d₆: δH 2.50 ppm, δC 39.5 ppm) as an internal reference. Flash chromatography was performed with silica gel (230–400 mesh), and thin-layer chromatography (TLC) was performed with glass-backed silica gel plates and visualized with UV (254 nm). IR spectra were measured utilizing an infrared spectrometer fitted with an ATR (attenuated total reflectance). High resolution mass spectra (HRMS) were obtained using a double-focusing magnetic sector (DFS) mass spectrometer for electron impact ionization (EI) and a Fourier transfer ion cyclotron resonance (FTICR) mass spectrometer for electrospray ionization (ESI). All yields are for materials obtained after chromatography, trituration, or recrystallization unless otherwise noted.

**General Method A for Preparation of Amidoesters 8.** A solution of the free amine of ethyl glycinate was generated using a modified procedure.³³ A mixture of ethyl glycinate hydrochloride (6.28 g, 45.0 mmol) in deionized water (100 mL) was treated with potassium carbonate (12.4 g, 90.0 mmol). The mixture was extracted with CH₂Cl₂ (5 × 50 mL). The organic layer was dried over sodium sulfate and used directly in the next reaction. Next, following a modified procedure,³⁴ the previously obtained solution of ethyl glycinate in CH₂Cl₂ was combined with an arylacetic acid (30.0 mmol) and then treated with DMAP (0.367 g, 3.0 mmol) followed by DCC (7.43 g, 36.0 mmol). The reaction mixture was stirred at rt until TLC analysis (EtOAc) showed complete consumption of the starting material. The reaction mixture was filtered, and the solid DCU residue was washed with CH₂Cl₂. Approximately half of the solvent was
removed in vacuo and then cooled and filtered to remove additional DCU. The organic layer was removed in vacuo gave oils or amorphous solids. Trituration (ether) gave the desired products as powders that were used directly without any further purification.

**Ethyl 2-(4′-methoxyphenyl)acetamidato)acetate (8b).**<br>White powder (5.03 g, 20.0 mmol, 77% yield): mp 124–125 °C; Rf 0.33 (15:85 MeOH/EtOAc); IR (ATR, neat) 1736, 1612 cm⁻¹; 1H NMR (400 MHz, DMSO-δ6) δ 7.17 (d, 4H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.44 (s, 2H), 4.23 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.49 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz) ppm; 13C NMR (100 MHz, DMSO-δ6) δ 174.4, 169.2, 158.7, 152.4, 130.0, 127.4, 114.0, 82.4, 61.5, 55.5, 48.8, 43.5, 28.1, 14.4 ppm; HRMS (EI-DFS) calc for C₁₅H₁₈F₃NO₇S 305.1263, found 305.1255.

**Ethyl 2-(3′,4′-dimethoxyphenyl)acetamidato)acetate (8d).**<br>White powder (3.62 g, 10.0 mmol, 65% yield): mp 124–125 °C; Rf 0.33 (15:85 MeOH/EtOAc); IR (ATR, neat) 1736, 1612 cm⁻¹; 1H NMR (400 MHz, DMSO-δ6) δ 7.17 (d, 4H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.44 (s, 2H), 4.23 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.49 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz) ppm; 13C NMR (100 MHz, DMSO-δ6) δ 174.4, 169.2, 158.7, 152.4, 130.0, 127.4, 114.0, 82.4, 61.5, 55.5, 48.8, 43.5, 28.1, 14.4 ppm; HRMS (EI-DFS) calc for C₁₅H₁₈F₃NO₇S 305.1263, found 305.1255.

**Ethyl 2-(N-(tert-butoxycarbonyl)-2-(4′-methoxyphenyl)acetamidato)acetamidato)acetate (9b).**<br>Yellow oil (10.6 g, 50.0 mmol, 87% yield): Rf = 0.48 (1:4 EtOAc/petrol ether); IR (ATR, neat) 1736, 1691, 1612 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.17 (d, 4H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.44 (s, 2H), 4.23 (s, 2H), 4.18 (q, 2H, J = 7.2 Hz), 3.78 (s, 3H), 1.49 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz) ppm; 13C NMR (100 MHz, CDCl₃) δ 174.3, 169.2, 159.8, 152.4, 136.5, 129.5, 122.2, 115.4, 112.8, 84.3, 61.5, 55.5, 45.9, 44.4, 28.1, 14.4 ppm; HRMS (EI-DFS) calc for C₁₇H₂₂NO₇S 351.1682, found 351.1688.

**Ethyl 2-(N-(tert-butoxycarbonyl)-2-(3′,4′-dimethoxyphenyl)acetamidato)acetamidato)acetate (9c).**<br>Colorless oil (3.62 g, 10.8 mmol, 65% yield): mp 124–125 °C; Rf = 0.33 (15:85 MeOH/EtOAc); IR (ATR, neat) 1736, 1691, 1612 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.22 (t, 1H, J = 7.4 Hz), 6.78–6.85 (m, 3H), 4.45 (s, 2H), 4.28 (s, 2H), 4.19 (q, 2H, J = 7.4 Hz), 3.79 (s, 3H), 1.48 (s, 9H), 1.26 (s, 3H, J = 7.2 Hz) ppm; 13C NMR (100 MHz, CDCl₃) δ 174.3, 169.2, 159.8, 152.4, 136.5, 129.5, 122.2, 115.4, 112.8, 84.3, 61.5, 55.5, 45.9, 44.4, 28.1, 14.4 ppm; HRMS (EI-DFS) calc for C₁₇H₂₂NO₇S 351.1682, found 351.1688.

**Ethyl 2-(N-(tert-butoxycarbonyl)-2-(3′,4′-dimethoxyphenyl)acetamidato)acetate (9d).**<br>Yellow oil (5.03 g, 14.4 mmol, 81% yield): Rf = 0.24 (1:4 EtOAc/petrol ether); IR (ATR, neat) 1736, 1691, 1612 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.22 (t, 1H, J = 7.4 Hz), 6.78–6.85 (m, 3H), 4.45 (s, 2H), 4.28 (s, 2H), 4.19 (q, 2H, J = 7.4 Hz), 3.79 (s, 3H), 1.48 (s, 9H), 1.26 (s, 3H, J = 7.2 Hz) ppm; 13C NMR (100 MHz, CDCl₃) δ 174.3, 169.2, 159.8, 152.4, 148.9, 148.2, 127.6, 122.0, 113.1, 111.3, 84.2, 61.5, 56.2, 56.1, 45.9, 43.8, 28.1, 14.5 ppm; HRMS (ESI-DFS) calc for C₁₇H₂₂NO₇S Na–Boc 304.1155, found 304.1155.
1-(tert-Butyloxy carbonyl)-3-(3′-methoxyphenyl)-4-((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (11c).

Yellow amorphous solid (0.424 g, 0.969 mmol, 30% yield): mp 84–86 °C; Rf = 0.50 (1:5 EtOAc/petroleum ether); IR (ATR, neat) 1774, 1703, 1687, 1607 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (t, 1H, J = 8.2 Hz, 2H), 7.23–7.25 (m, 2H), 6.97 (dd, 1H, J = 1.2, 2.4, 8.2 Hz), 4.59 (2H, 3.82 (3H, 1.59 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 164.6, 159.9, 154.9, 149.1, 130.0, 127.3, 124.4, 118.3, 111.6, 116.6, 114.0, 84.5, 55.6, 47.8, 28.3 ppm; HRMS (ESI-FTICR) calc'd for C₂₉H₂₆NO₅SNa 460.0648, found 460.0648.

1-(tert-Butyloxy carbonyl)-3′,4′-dimethoxyphenyl)-4-((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (11d).

White powder after trituration with EtOH (1.78 g, 3.80 mmol, 64% yield); triturated (EtOH) gave the analytical sample as a white powder: mp 103–105 °C; Rf = 0.20 (1:6 EtOAc/petroleum ether); IR (ATR, neat) 1788, 1706, 1677, 1601 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35 (dd, 1H, J = 2.0, 8.4 Hz), 7.32 (dd, 1H, J = 2.0, 8.4 Hz), 6.92 (2H, J = 8.4 Hz), 4.56 (2H, 3.91 (3H, 3.89 (3H, 1.58 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 165.0, 153.5, 150.6, 149.1, 149.10, 123.9, 122.4, 118.9, 111.5 (g (J = 319 Hz), 111.7, 111.3, 84.6, 56.1, 56.15, 47.6, 28.3 ppm; HRMS (ESI-FTICR) calc'd for C₂₉H₂₆NO₅SNa 490.0754, found 490.0754.

General Method E for the Conversion of 11 into 12. To a rt stirred solution of triflate 11 (5.00 mmol) in CH₂Cl₂ (10 mL) was added TFA (10 mL). The reaction mixture was stirred until TLC (1:1 EtOAc/petroleum ether) showed consumption of the starting material. The solvent was removed in vacuo, and the crude product was taken up in CH₂Cl₂ (20 mL), and the organic solution was washed with brine (20 mL) and dried over sodium sulfate. Removal of the solvent in vacuo followed by trituration (EtOH) or flash chromatography (EtOAc/petroleum ether gradient) gave the desired products as powders or amorphous solids.

3′-4′-Dimethoxyphenyl)-4-((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (12b).

Tan amorphous solid (1.48 g, 4.39 mmol, 90% yield): reaction time = 6 h; mp 111–113 °C; Rf = 0.38 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3200, 1693, 1613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (br s, 1H), 7.64 (2H, J = 9.2 Hz), 7.05 (2H, J = 9.2 Hz), 4.32 (2H, J = 1.2 Hz), 3.80 (3H, 3ppm); ¹³C NMR (100 MHz, CDCl₃) δ 168.3, 159.9, 154.2, 129.8, 122.7, 119.5, 117.7 (g (J = 319 Hz), 114.0, 55.2, 44.4 ppm; HRMS (EI-DFS) calc'd for C₂₃H₂₀F₃NO₈S 437.0232, found 437.0228.

3′-3′-Methoxyphenyl)-4-((trifluoromethyl)sulfonyl)oxy)-1H-pyrrol-2(5H)-one (12c).

Yellow powder (1.06 g, 3.14 mmol, 98% yield): reaction time = 1 h; mp 108–110 °C; Rf = 0.39 (1:1 EtOAc/petroleum ether); IR (ATR, neat) 3208, 1686, 1608 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.78 (br s, 1H), 7.41 (t, 1H, J = 8.4 Hz), 7.20–7.23 (m, 2H), 7.03 (dd, 1H, J = 1.2, 2.4, 8.4 Hz), 4.35 (2H, J = 1.2 Hz), 3.77 (3H, 3.75 (3H, 3.89 (3H, 1.60 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 168.0, 159.0, 150.7, 129.7, 128.4, 123.0, 122.5, 120.6, 117.7 (g (J = 319 Hz), 114.9, 113.9, 55.1, 44.5 ppm; HRMS (EI-DFS) calc'd for C₂₀H₁₈F₃NO₅SNa 373.0232, found 373.0227.

3′-3′-Butoxycarbonyl)-3-(3′-methoxyphenyl)-1H-pyrrol-2(5H)-one (13c).

White amorphous solid (from 11c, Method G: 88 mg, 0.22 mmol, 45% yield; from 13c, Method G: 0.11 g, 0.28 mmol, 25% yield): mp 70–75 °C; Rf = 0.20 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1758, 1727, 1637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.21–7.27 (m, 2H), 6.82–6.93 (m, 6H), 4.62 (2H, 3.82 (3H, 3.81 (3H, 1.59 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 168.6, 159.9, 159.8, 150.2, 149.7, 133.5, 132.9, 132.7, 130.1, 129.8, 122.3, 120.3, 116.4, 119.2, 113.3, 83.4, 55.5, 55.4, 51.1, 28.4 ppm; HRMS (EI-DFS) calc'd for C₂₃H₂₀NO₅SNa 395.1733, found 395.1737.

3′-3′-Butoxycarbonyl)-3-(3′-methoxyphenyl)-1H-pyrrol-2(5H)-one (13c).

Yellow amorphous solid (from 11c, Method G: 88 mg, 0.22 mmol, 45% yield; from 13c, Method G: 0.11 g, 0.28 mmol, 25% yield): mp 70–75 °C; Rf = 0.20 (1:4 EtOAc/petroleum ether); IR (ATR, neat) 1758, 1727, 1637 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.21–7.27 (m, 2H), 6.82–6.93 (m, 6H), 4.62 (2H, 3.82 (3H, 3.81 (3H, 1.59 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 168.6, 159.1, 159.8, 150.5, 148.5, 131.2, 130.3, 129.6, 123.9, 114.4, 83.2, 55.6, 55.5, 50.9, 28.5 ppm; HRMS (EI-DFS) calc'd for C₂₃H₂₀NO₅SNa 395.1733, found 395.1737.
6.84 (m, 2H), 4.35 (d, 2H, J = 8.4 Hz), 6.90 (d, 2H, J = 8.0 Hz), 7.27 (m, 1H), 6.82–6.95 (m, 6H), 6.81–6.92 (m, 9H), 4.32 (d, 2H, J = 0.8 Hz), 3.74 (s, 3H), 3.76 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.6, 159.8, 159.0, 131.4, 130.0, 129.3, 129.0, 152.4, 121.6, 115.0, 114.0, 113.0, 55.2, 54.9, 47.3 ppm; HRMS (EI-DFS) calc for C18H17NO3 295.1208, found 295.1220.

3-(3′-Methoxyphenyl)-4-(4′-methoxyphenyl)-1H-pyrrole-2(5H)-one (15ac). Yellow amorphous powder (Method G: 0.268 g, 0.907 mmol, 61% yield): mp 223–227 °C (lit.38 mp 213–216 °C); Rf = 0.55 (1:9 MeOH/MeOH); IR (ATR, neat) 3174, 1627, 1607 cm⁻¹; H NMR (400 MHz, DMSO-d6) δ 8.41 (s, br, 1H), 7.27 (m, 1H), 7.06 (d, J = 9.0 Hz), 7.24–7.28 (m, 1H), 6.89 (d, 2H, J = 9.2 Hz), 4.29 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.7, 159.8, 150.7, 164.3, 149.0, 148.8, 146.1, 133.7, 131.2, 128.8, 128.6, 127.4, 124.9, 119.2, 119.5, 111.5, 55.4, 52.5, 47.7 ppm; HRMS (EI-DFS) calc for C19H17NO3 299.1260, found 299.1260.

3-(3′-Methoxyphenyl)-4-(4′-methoxyphenyl)-1H-pyrrole-2(5H)-one (15bb). Yellow amorphous powder (Method G: 0.240 g, 0.813 mmol, 55% yield): mp 223–227 °C (lit.36 mp 213–216 °C); Rf = 0.55 (1:9 MeOH/MeOH); IR (ATR, neat) 3174, 1672, 1626 cm⁻¹; H NMR (400 MHz, DMSO-d6) δ 8.41 (s, br, 1H), 7.27 (m, 1H), 7.06 (d, J = 9.0 Hz), 7.24–7.28 (m, 1H), 6.89 (d, 2H, J = 9.2 Hz), 4.29 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.7, 159.8, 150.7, 164.3, 149.0, 148.8, 146.1, 133.7, 131.2, 128.8, 128.6, 127.4, 124.9, 119.2, 119.5, 111.5, 55.4, 52.5, 47.7 ppm; HRMS (EI-DFS) calc for C19H17NO3 299.1260, found 299.1260.

3-(3′-Methoxyphenyl)-4-(4′-methoxyphenyl)-1H-pyrrole-2(5H)-one (15bc). Yellow amorphous powder (Method G: 0.240 g, 0.813 mmol, 55% yield): mp 223–227 °C (lit.36 mp 213–216 °C); Rf = 0.55 (1:9 MeOH/MeOH); IR (ATR, neat) 3174, 1672, 1626 cm⁻¹; H NMR (400 MHz, DMSO-d6) δ 8.41 (s, br, 1H), 7.27 (m, 1H), 7.06 (d, J = 9.0 Hz), 7.24–7.28 (m, 1H), 6.89 (d, 2H, J = 9.2 Hz), 4.29 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.7, 159.8, 150.7, 164.3, 149.0, 148.8, 146.1, 133.7, 131.2, 128.8, 128.6, 127.4, 124.9, 119.2, 119.5, 111.5, 55.4, 52.5, 47.7 ppm; HRMS (EI-DFS) calc for C19H17NO3 299.1260, found 299.1260.
Brown powder (21 mg, 0.065 mmol, 42% yield): mp 165°C.

1H, 13C NMR (100 MHz, DMSO-d6): δ 8.44 (br s, 1H), 8.67–8.69 (m, 3H), 6.65 (s, 2H), 4.34 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.59 (s, 6H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.6, 152.7, 149.3, 148.5, 148.3, 138.0, 131.1, 128.7, 124.8, 122.0, 113.1, 111.7, 105.3, 60.0, 55.7, 55.5, 55.4, 47.4 ppm; HRMS (EI-DFS) calcd for C24H22NO6: 439.1525, found 439.1523.

**General Method I for the Oxidative Cyclization to Dibenzo[e]isoindole-1-ones 16.** To a 40°C stirred solution of 1S (1.00 mmol) and PIFA (0.473 g, 1.10 mmol) in CH2Cl2 (10 mL) was added BF3·Et2O (0.15 mL, 1.2 mmol). The reaction mixture was stirred at 196°C for 0.50 (EtOAc solvent); IR (ATR, neat) 3183, 1681, 1607 cm−1; 1H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.59 (s, 1H), 8.07 (s, 2H), 7.56 (s, 1H), 4.67 (s, 2H), 4.07 (s, 3H), 4.05 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 172.3, 152.6, 152.7, 150.3, 149.7, 141.2, 131.0, 125.7, 124.9, 122.4, 121.9, 121.6, 110.5, 105.0, 104.5, 56.0, 55.7, 55.5, 43.9 ppm; HRMS (EI-DFS) calcd for C24H22NO6: 439.1525, found 439.1523.

2,3-Dihydro-9,10-dimethoxy-1H-dibenzo[e]isoindole-1-one (16c). Brown powder (14 mg, 0.048 mmol, 45% yield): mp 275–280°C; Rf = 0.50 (EtOAc solvent); IR (ATR, neat) 3201, 1682, 1615 cm−1; 1H NMR (400 MHz, DMSO-d6) δ 8.70–8.75 (m, 4H), 7.39–7.47 (m, 2H), 7.33 (dd, 1H, J = 2.8, 8.8 Hz), 4.70 (s, 2H), 4.05 (s, 3H), 3.94 (s, 3H) ppm; 13C NMR (100 MHz, DMSO-d6) δ 171.9, 157.7, 156.9, 147.5, 127.7, 127.5, 126.7, 125.7, 125.0, 124.5, 124.3, 124.2, 119.0, 117.0, 104.9, 104.1, 55.5, 55.2, 44.0 ppm; HRMS (EI-DFS) calcd for C24H21NO5: 387.1572, found 387.1570.

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