Synthesis of Imidazol[1,5-*a*]indole-1,3-diones from Imidazolidene-2,4-diones

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ABSTRACT

Copper and tributyltin hydride catalysed cyclization, through the *N*-aryl bond formation, of imidazolidine-2,4-diones (11–16,18**) yielded imidazo[1,5-*a*]indole-1,3-diones (**5–10**) in high yields (72–100%). The ease of cyclization was found to be consistent with the normal halogen reactivity and the type of substituents. The highly substituted imidazole-2,4-dione** 15 **gave brominated** 19 **and tin incorporated heterocycles** 20 **when treated with copper bromide and tributyltin hydride, respectively.**

KEYWORDS

Indoles, imidazolidine-2,4-diones, arylaldehyhydes, copper bronze, tributyl tin hydride.

1. Introduction

Indoles of varying complexity have profound biological activity and significance in medicinal chemistry.[1,2] For example, amauromine is a vasodilator,[3] while indomethacin is used in the treatment of rheumatoid arthritis.[4] 5-*N*-acetylardeemin is one of the most potent known agents for reversal of multiple drug resistance,[5] lysergic acid diethylamide is physiologically active and indole-3-acetic acid has well-known plant growth regulatory properties.[4] Currently, intensive research to identify potent viable drugs for management of AIDS has resulted into identifying indoles to be among the non-nucleoside reverse transcriptase inhibitors (NNRTI). In fact, the most effective anticancer and anti-HIV drugs are derived from the indole basic structure, with substituents in both the aromatic and heterocyclic rings.[6–9]

As a consequence of this widespread bioactivity, many methods of indole synthesis have been developed. These methods can be classified broadly into two categories: those in which the *N*-aryl bond is established at an early stage and those involving the *N*-aryl bond formation late in the synthesis. Superimposed onto each of these is a strategy that depends upon assembly of the benzenoid ring. The better known and more widely used methods include the Fischer,[10] Bischler,[11] Reissert,[12] Madelung,[13] and Batcho-Leimgruber[1] indole syntheses. In all the above methods, the pyrrole ring is constructed by annulation on to an appropriately nitrogen-substituted aromatic precursor. Thus the bond between the nitrogen and the benzene ring is established very early in the synthesis. There are few syntheses of indoles that involve formation of the *N*-aryl bond. These include Nenitzescu[14] indole synthesis, copper catalysed ring closure,[15] Bartoli synthesis[16] and the Pd-catalysed tandem C-N/Suzuki-Miyaura coupling.[17]

The search for an efficient synthesis of indoles has been a problem for nearly a century in organic synthesis and only the Batcho-Leimgruber[1] method provides a general route for synthesizing indoles, which are substituted on the benzene ring but not on the heterocyclic nucleus. In our effort to contribute to the synthesis of this class of compounds, we hereby present a new, efficient method for synthesizing indoles that are substituted in both the benzene and the heterocyclic rings, in two steps. The steps involve the initial condensation of aromatic aldehydes **1** with imidazolidine-2,4-diones[18] **2a** and **2b** followed by cyclization of the generated 5-[phenylmethyledene]-imidazolidine-2,4-diones **3,4** (Scheme 1). Cleavage of the hydantoin ring can be a potential route to 2-substituted indoles. This is important because indoles are more reactive at the 3-position, and will react at this position before substituents can be added as electrophiles, to the 2-position.

2. Results and Discussion

It was anticipated that problems could arise during the attempted cyclization due to the presence of two acidic NH groups in imidazolidine-2,4-dione (hydantoin) itself. Though the more acidic nitrogen at position 3 cannot be involved in intramolecular cyclization, such acidic sites might lead to intermolecular reactions and polymers.[19] In order to overcome these problems, imidazolidine-2,4-diones protected at position 3 were synthesized. The protecting groups used were the readily available phenyl and methyl groups, though other protecting groups have been reported.[20]

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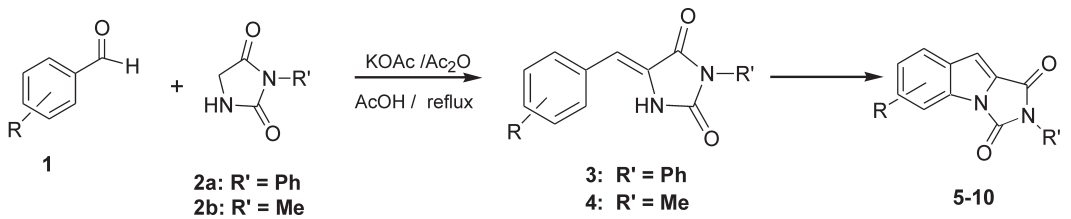
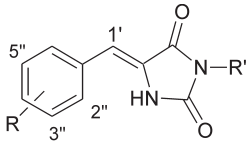


Scheme 1
Synthesis of indoles.

Table 1 Yield and isomer ratio of 5-[phenylmethyledene]imidazolidine-2,4-diones **11–16** and **18**.



11-16, 18

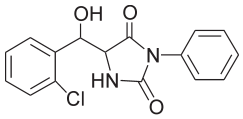
	Substituent position							
Product	Time/h	R′	R2″	R3″	R4″	R5″	%Yield	(Z):(E)
11	8	Ph	Br	H	H	H	64	100:0
12	5	Ph	Cl	H	H	H	64	90:10
13	5	Ph	Cl	H	OH	H	24	100:0
14	16	Ph	Br	H	OMe	OMe	19	100:0
15	16	Ph	Br	OMe	OMe	OMe	34	100:0
16	5	Ph	Cl	H	H	NO_2	61	90:10
18 [a]	16	Me	Cl	H	H	H	85	70:30

[a] A stochiometric amount of Ac_2O.

The precursor, 3-phenylimidazolidine-2,4-dione **2a**, was synthesized from glycine and phenylisocyanate,[21] while 3-methyl-1,3-diazolidine-2,4-dione **2b** was prepared according to the method of Harris and Weiss.[22]

Condensation reactions, between aldehydes and **2a**, were carried out under standard conditions of reflux in glacial acetic acid, in the presence of potassium acetate and a little acetic anhydride (Table 1).[21,23] The assignment of geometric isomers was carried out by comparing the chemical shifts of their olefinic proton signals,[23] and confirmed through Nuclear Overhauser enhancement (NOESY) NMR experiments. The (*Z*)-isomer was the major isomer, probably because it is thermodynamically more stable than the (*E*)-isomer. Electron donating groups on the aldehyde retard the initial addition process, while the same groups speed the dehydration reaction up by stabilizing the incipient cationic charge at the benzylic center.[23] The lower yields of **13, 14,** and **15** may be an indication that the first step, addition, was rate limiting.

3-Methyl-1,3-diazolidine-2,4-dione **2b** was condensed with 2-chlorobenzaldehyde, in the presence of potassium acetate and a catalytic amount of acetic anhydride, to yield the intermediate



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alcohol **17** as one stereoisomer. The reaction was repeated using stoichiometric amounts of acetic anhydride to yield **18**.

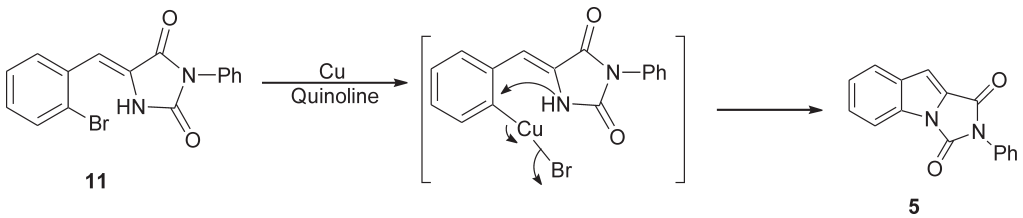
Copper-catalysed cyclization[23,24] of 2-halo substrates, **11–15** and **18** under reflux conditions in quinoline gave, after work-up and chromatographic purification, fluorescent products **5–9**, (Table 2). All the products showed a change from the olefinic proton signal to a narrow aromatic doublet.[23] Absence of the NH signal in their ^{1}H NMR spectra, was also used to confirm cyclization.

The precise mechanism of cyclization is not known; however, it probably involves an intermediate in which copper, *via* copper (I), has inserted into the aryl halide bond, followed by a nucleophillic substitution of the nucleophilic nitrogen group (Scheme 2). Insertion of copper was part of the rate determining

Table 2 Yield and physical properties of imidazol[1,5-*a*]indole-1,3-diones **5–10**.

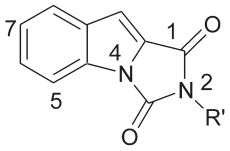
Phenylmethyledeneimidazolidine-2,4-diones	Time/h	Imidazol[1,5-a]indole-1,3-dione	m.p/°C	Yield/%
11	2	**5**	198-200	80
12	0.2	**5**	198-200	72
13	1	**6**	248-249	100
14	0.3	**7**	244-246	98
15	1	**8**	210–212	50
18	1	**9**	243–245	75
16 [b]	0.5	**10**	258–260	73

[b] Cu/DMF.

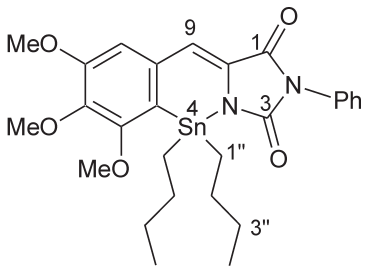


11 **5**

Scheme 2
Proposed mechanism of cyclization.



5: $R^5 = R^6 = R^7 = R^9 = R^9 = H$, R' = Ph
6: R^6 = OH, $R^5 = R^7 = R^9 = H$; R' = Ph
7: $R^6 = R^7$=OMe; $R^5 = R^8 = R^9 = H$, R' = Ph
8: $R^5 = R^6 = R^7$ =OMe; $R^8 = R^9 = H$; R' = Ph
9: $R^5 = R^6 = R^7 = R^8 = R^9 = H$; R' = Me
10: $R^5 = R^6 = R^8 = R^9 = H$; $R^7 = NO_2$, R' =Ph
19: $R^5 = R^6 = R^7$ =OMe; R^8 = Br; R^9 = H; R' = Ph



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step of the reaction, since hindrance about this center decreased the yield, either through slower copper insertion or interferance with ring closure of the aryl copper intermediate. The ease of cyclization was consistent with the normal halogen reactivity of the substrates.

Efforts to cyclize **16** under similar conditions were unsuccessful and suggested that other factors might influence the reaction. The solvent, quinoline, was replaced with dimethyl formamide (DMF) and the reaction performed at reflux in the presence of only a catalytic amount of copper bronze[25] to give **10**. Electron withdrawing groups *ortho*- or *para*- to the halogen have been known to hasten Ullmann reactions.[24] Similar treatment of **15** gave the unexpected product **19**, which might have been derived from oxidative cyclization at the non-brominated position.

Compounds **11, 12,** and **14**, were each treated at reflux temperature with tributyltin hydride, in presence of AIBN as the radical initiator, to yield **5** and **7** (Table 3). This result is consistent with the lower reactivity of organochlorine compounds compared with organobromine reactants in free radical reactions. Most probably, an aryl radical was generated and would have undergone intramolecular cyclization.

The unique reaction of the 2-bromo-3,4,5-trimethoxy precursor, **15**, was again demonstrated when this precursor yielded the unexpected tin incorporated heterocycle, **20**. In the ^{1}H NMR spectrum of **20**, scalar coupling to the tin nucleus was only observed for the H9 proton and not to the H4 proton. This indicated that the molecule is planar and rigid, the path between H9 and tin is a W-shape and should provide more favourable coupling than the alternative path between H4 and the tin. The ^{13}C NMR spectrum of **20**, showed 27 signals. The signals at 26.0 and 27.7, corresponding to the methylene carbons attached to the tin exhibited tin satellites (*J* 69.0, 22.6 Hz, respectively). The most likely explanation for these latter observations was that **20** was in a conformationally locked, square planar arrangement that made the butyl groups non-equivalent. Indeed tin is known to exhibit either a tetrahedral or square planar conformation. When the two butyl groups are non-equivalent, as observed for **20**, it appears logic that tin should be in a planar conformation. The exact conformation can only be determined using X-ray crystallography. The *N*-phenyl ring was influenced by the tin that all its carbons were now non-equivalent.

3. Experimental

3.1. General

Melting points were measured on a Reichert microscope and are uncorrected. ^{1}H NMR spectra were recorded in dimethyl sulfoxide (DMSO) on a Bruker DMX 500 (500 mHz) Avance instrument. Data are reported as follows: chemical shift (δ) in ppm downfield from tetramethylsilane (TMS), number of protons, multiplicity, observed coupling constant(s) (*J* in Hz) and proton assignment. Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), broad doublet (br d), doublet of doublets (dd), triplet (t), multiplet (m). The ^{13}C NMR spectra were also recorded on a Bruker AC 300F spectrometer at 75.06 mHz and are reported in ppm downfield from TMS. The electron impact (EI) mass spectra were recorded on a VG Quattro mass spectrometer with an ionizing potential of 70 eV and an ion source temperature of 220°C. The principal ion peaks *m/z* are reported together with their percentage intensities relative to the base peak. HRMS were recorded on a Bruker Daltonics (Bellerica, MA), BiopAPEX II 7T FT/ICR mass spectrometer.

3-Phenylimidazolidine-2,4-dione (**2a**)[23,26]

Glycine (7.5 g g, 0.13 mol) was dissolved into a solution of KOH (6.80 g) in water (40 mL) and the mixture cooled in ice. Phenylisocyanate (13.20 g, 0.11 mol) was added dropwise to the stirred solution. Upon standing overnight, the mixture deposited a precipitate (2.00 g) that was collected and identified as diphenyl urea m.p. 235–237°C, (lit.[26] m.p. 239–241°C). The filtrate was acidified to yield another precipitate which was collected, drained at the pump, then refluxed with a mixture of water (20 mL) and HCl (50%, 20 mL) for 1 h. The resulting solution was cooled to room temperature and the crystalline precipitate was collected. Further recrystallization from ethanol gave **2a** as white needles (11.60 g, 66%, m.p. 153–154°C (lit.[26] m.p. 154–155°C).

3.2. Condensation Reactions of 2a with Aldehydes

General Procedure for Condensation Reactions[26]

Molar equivalents of compound and the aldehydes, anhydrous NaOAc or KOAc, glacial AcOH and Ac_2O (3 drops) were

Table 3 Yield of imidazol[1,5-*a*]indole-1,3-diones **5** and **7** using tributyl tin hydride.

Phenylmethyledeneimidazolidine-2,4-diones	Time/h	Imidazol[1,5-a]indole-1,3-dione	Yield/%
11	3	**5**	99
12	8	**5**	68
14	3	**7**	89

dissolved together at r.t. and the mixture warmed to reflux temperature. Reactions were monitored by thin layer chromatographic analysis until all the aldehyde had reacted. Upon cooling, the mixture gave a precipitate which was collected and recrystallized.

5-[(Z)-1-(2-Bromophenyl)methylidene]-3-phenylimidazolidine-2,4-dione (**11**)

Bromobenzaldehyde (4.00 g, 21.6 mmol) reacted after 8 h to give a yellow solid (5.00 g) that was shown by ^{1}H NMR to be isomerically pure. Recrystallization from AcOH gave **11** as white needles (4.88 g, 64%), m.p. 240–242°C; δ_H (500 MHz, DMSO-d_6) 6.70 (1H, s, 1′-H), 7.29 (2H, dd, *J* 8.2, 2.0 Hz, 4″-H and 5″-H), 7.40–7.50 (4H, m, 2‴-H to 6‴-H), 7.75 (2H, dd *J* 8.2, 2.0 Hz, 3″- and 6″-H), 11.13 (1H, br s, 1-NH); δ_C (500 MHz, DMSO-d_6 107.6 (C-1′), 124.5 (C-2″), 127.2 (C-2‴ and C-6‴), 128.4 (C-5), 128.5 (C-4‴), 129.0 (C-5″), 129.2 (C-3‴ and C-5‴), 130.7 (C-6″), 130.8 (C-1″), 132.0 (C-4″), 132.1 (C-1‴), 132.9 (C-3″), 154.4 (C-2), 163.3 (C-4); *m/z* 345 (M(^{81}Br)+1, 4%), 344 (M(^{81}Br)$^+$, absent), 343 (M(^{79}Br)+1, 4), 265 (4), 264 (22), 263 (100), 262 (6), 195 (6), 144 (3), 132 (5), 119 (24), 115 (39), 114 (16), 89 (40), 77 (17), 65 (7), 63 (16), 51 (4); (Found: C, 56.11; H, 2.96; N, 8.11. $C_{16}H_{11}N_2BrO_2$ requires: C, 56.00; H, 3.23; N, 8.16%).

5-[(Z)-and (E)*-1-(2-Chlorophenyl)methylidene]-3-phenyl-imidazolidine-2,4-dione* (**12**)[25]

2-Chlorobenzaldehyde (5.00 g, 36 mmol) reacted after 5 h to give a yellow solid (4.90 g). Recrystallization from EtOH gave a 90:10 mixture of (*Z*)- and (*E*)-**12** as white needles (4.73 g, 64%), m.p. 250–252°C (lit.[25] 252–253°C).

5-[(Z)-1-(2-Chloro-4-hydroxyphenyl)methylidene]-3-phenyl-imidazolidine-2,4-dione (**13**)

2-Chloro-4-hydroxybenzaldehyde, (2.00 g, 13 mmol), reacted after 5 h to give a yellow solid (0.94 g) that was identified by ^{1}H NMR as a single isomer. Recrystallization from AcOH gave **13** as yellow needles (0.78 g, 24%), m.p. 240–242°C; δ_H (500 MHz, DMSO-d_6) 6.73 (1H, s, 1′-H), 6.83 (1H, dd, *J* 8.6, 2.5 Hz, 5″-H), 6.95 (1H, d, *J* 2.5 Hz, 3″-H), 7.41–7.52 (4H, m, 2‴-H to 6‴-H), 7.67 (1H, d, *J* 8.6 Hz; 6″-H), 10.35 (1H, br s, 1-NH), 10.97 (1H, s, 4″-OH); δ_c(500 MHz, DMSO-d_6) 105.7 (C-1′), 115.2 (C-5″), 116.6 (C-3″), 121.7 (C-1″), 126.6 (C-4‴), 127.3 (C-2‴ and C-6‴), 128.2 (C-5), 129.2 (C-3‴ and C-5‴), 131.3 (C-6″), 132.1 (C-1‴), 134.7 (C-2″), 154.4 (C-2), 159.1 (C-4″), 163.3 (C-4); *m/z*: 316 (M+1, 0.3%), 315 (M$^+$, 0.5), 279 (39), 168 (6), 167 (18), 166 (15), 130 (130), 119 (80), 105 (32), 91 (100), 77 (58), 76(31), 65 (22) 64 (45), 63 (31), 51 (42); (Found: C, 60.99; H, 3.56; N, 8.93. $C_{16}H_{11}ClN_2O_3$ requires: C, 60.99; H, 3.52; 8.90%).

5-[(Z)-1-(2-Bromo-4,5-dimethoxyphenyl)methylidene]-3-phenyl-imidazolidine-2,4-dione (**14**)

2-Bromo-4,5-dimethoxybenzaldehyde reacted after 16 hours to give a yellow solid (3.00 g) that was collected and shown by ^{1}H NMR to be isomerically pure. Recrystallization from MeOH gave **14** as yellow needles (2.90 g, 19%), m.p. 288–290°C; δ_H (500 MHz, DMSO-d_6) 3.80 (3H, s, 5″-OCH_3), 3.87 (3H, s, 4″-OCH_3), 6.63 (1H, s, 1′-H), 7.14 (1H,s, 6″-H), 7.25 (1H, s, 3″-H), 7.42 (2H, tm, *J* 7.2 Hz, 2‴-H and 6‴-H), 7.47 (1H, tm, *J* 7.2 Hz, 4‴-H), 7.56 (2H, tm, *J* 7.2 Hz, 3‴-H and 5‴-H), 11.11 (1H, br s, NH); δ_C (500 MHz, DMSO-d_6) 56.0 (4″-OCH_3), 56.4 (5″-OCH_3), 108.6 (C-1′), 112.8 (C-6″), 115.7 (C-2″), 116.0 (C-3″), 124.7 (C-1″), 127.3 (C-2‴ and C-6‴), 127.5 (C-4‴), 128.4 (C-5), 129.2 (C-3‴ and C-5‴), 132.1 (C-1‴), 148.5 (C-4″), 150.2 (C-5″), 154.4 (C-2), 163.3 (C-4); *m/z* 404 (M$^+$, 5%), 325, (5), 324 (10), 323 (100), 307 (10), 279 (5), 240 (5), 176 (5), 162 (10), 149 (5), 133 (5), 119 (10), 102 (5), 91 (10), 77 (10), 63 (10), 51 (3). (Found: C, 53.82; H, 3.87; N, 6.75. $C_{18}H_{15}BrN_2O_4$ requires: C, 53.61; H, 3.74; N, 6.94%).

5-[(Z)-1-(2-Bromo-3,4,5-trimethoxyphenyl)methylidene]-3-phenyl-imidazolidine-2,4-dione (**15**)

2-Bromo-3,4,5-trimethoxybenzaldehyde reacted after 16 h to give a yellow solid (3.65 g) that was shown by ^{1}H NMR to be isomerically pure. Recrystallization from MeOH gave **15** as yellow needles (3.50 g, 34%), m.p. 260–262°C; δ_H (500 MHz, DMSO-d_6) 3.79 (3H, s, 4″-OCH_3), 3.80 (3H, s, 3″-OCH_3), 3.91 (3H, s, 5″-OCH_3), 6.61 (1H, s, 1′-H), 7.16 (1H, s, 6″-H), 7.33–7.52 (5H, m, 2‴-H to 6‴-H), 11.20 (1H, br s, NH); δ_C (500 MHz, DMSO-d_6) 56.4 (5″-OCH_3), 61.2 (3″-OCH_3 and 4″-OCH_3), 107.7 (C-1′), 109.6 (C-6″), 110.8 (C-2″), 127.2 (C-2‴ and C-6‴), 128.3 (C-5), 128.8 (C-4‴), 129.2 (C-3‴ and C-5‴), 129.9 (C-1‴), 132.3 (C-1″), 143.1 (C-4″), 150.9 (C-2), 152.9 (C-3″), 155.0 (C-5″), 163.7 (C-4); *m/z* 434 (M$^+$ (^{81}Br), 5%), 432 (m(^{79}Br), 5), 354 (30), 353 (100), 323 (10), 292 (15), 176 (22), 120 (10), 119 (22); (Found: C, 52.00; H, 3.70; N, 6.30. $C_{19}H_{17}BrN_2O_5$ requires: C, 52.70; H, 4.00; N, 6.50%).

5-[(Z)-and (E)*-1-(2-Chloro-5-nitrophenyl)methylidene]-3-phenylimidazolidine-2,4-dione* (**16**)

2-Chloro-5-nitrobenzaldehyde (4.60 g, 25 mmol), reacted after 5 h to give a white solid (5.60 g). Recrystallization from acetic acid gave a 60:40 mixture (*Z*):(*E*) isomers of **16** as white needles (5.30 g, 61%), m.p. 205–206°C; δ_H (500 MHz, DMSO-d_6) 6.49 (1H, s, 1′-H, *E*-isomer), 6.60 (1H, s, 1′-H, *Z*-isomer), 7.33–7.53 (4H, m, 2‴-H to 6‴-H), 7.80 (1H, d, *J* 8.7 Hz, 3″-H), 8.17 (1H, dd, *J* 8.7, 2.6 Hz, 4″-H), 8.45 (1H, d, *J* 2.6 Hz, 6″-H), 9.12 (1H, br s, 1-NH, *Z*-isomer), 9.50 (1H, br s, 1-NH, *E*-isomer); δ_C (500 MHz, DMSO-d_6) 102.6 (C-1′); 124.4 (C-4″), 125.6 (C-6″), 125.7 (C-5); 127.2 (C-2‴ and C-6‴); 128.5 (C-4‴); 129.2 (C-3‴ and C-5‴); 131.1 (C-1‴); 132.1 (C-3″); 133.1 (C-1″); 139.7 (C-2″); 146.9 (C-5″); 154.8 (C-2); 163.2 (C-4); *m/z* 346 (M(^{37}Cl)$^{+1}$, 0.5%), 345 (M(^{37}Cl)$^+$, 0.4), 344 (M(^{35}Cl)+1, 0.2), 343 (M(^{35}Cl)+1, 0.4), 308 (7), 262 (3), 196 (5), 179 (6), 150 (18), 125 (20), 123 (64), 119 (42), 114 (38), 91 (100), 77 (92), 65 (38), 64 (55), 63 (55), 51 (63); (Found: C, 55.88; H, 3.14; N, 12.16. $C_{16}H_{10}ClN_3O_4$ requires: C, 55.90; H, 2.91; N, 12.22%).

3-Methyl-1,3-diazolidine-2,4-dione (**2b**)[22]

Imidazolidine-2,4-dione (8.00 g, 0.04 mol) and dimethyl sulfate (10.00 g, 0.04 mol) were dissolved in NaOH (50 mL, 2 M) and the solution stirred at r.t. overnight. The mixture was poured into water (50 mL) and neutralized with HCl (2 M). The resulting solution was extracted with EtOAc (3 × 20 mL) and the combined organic extracts dried over $MgSO_4$. Excess solvent was evaporated off under reduced pressure to afford a white solid (2.70 g). The solid was recrystallized from EtOH to give **2b** as white needles (2.50 g, 55 %), m.p. 158–160°C (lit.[22] m.p. 155–157°C).

5-[2-Chlorophenyl)(hydoxy)methyl]-3-methylimidazolidine-2,4-dione (**17**)

Diazolidine **2a** (1.00 g, 0.877 mmol), 2-chlorobenzaldehyde (1.50 g, 1.07 mmol), KOAc (3.00 g), Ac_2O (3 drops) were heated at reflux for 8 h. Upon cooling the reaction mixture gave a white solid which was recrystallized from EtOH to afford **17** as white needles (0.15 g, 67%), m.p. 212–213°C; δ_H (500 MHz, DMSO-d_6) 2.83 (3H, s, CH_3), 4.24 (1H, s, OH), 5.28 (1H, dd, *J* 5.6, 3.0 Hz, 1′-H), 5.90 (1H, d, *J* 5.6, 5-H), 7.32–7.35 (3H, m, 4″-H to 6″-H), 7.60 (1H, dd, *J* 7.2, 2.0 Hz, 3″-H), 7.80 (1H, br s, NH); δ_C (500 MHz, DMSO-d_6) 24.2 (CH_3), 60.9 (C-1′), 67.7 (C-5), 127.5 (C-6″), 129.0 (C-3″, C-4″ and C-5″), 130.5 (C-1″), 138.7 (C-2″), 158.1 (C-2) 172.7

(C-4); *m/z* 257 (M(^{37}Cl)+1, 0.8), 256 (M(^{37}Cl)$^{+1}$, 0.5), 255 (M(^{35}Cl)+1, 2%) 254 (M(^{35}Cl)$^{+1}$, absent), 239 (0.8), 237 (2), 201 (21), 177 (9), 176 (70), 143 (10), 141 (36), 120 (14), 119 (49), 114 (100), 113 (28), 77 (19), 51 (24); (Found: C, 51.96; H, 4.20; N, 11.03. $C_{11}H_{11}ClN_2O_3$ requires: C, 51.96; H, 4.31; N, 10.98%).

5-[(Z)- and (E)-1-(2-chlorophenyl)methylidene]-3-methyl-imidazolidine-2,4-dione (**18**)[27]

The reaction was repeated with a volumetric amount of Ac_2O (5 mL) and the reaction heated at reflux for 16 h. Upon cooling a white solid was obtained that was recrystallized from EtOH to afford 70: 30 mixture of (*Z*)- and (*E*)-**18** as white needles (0.18 g, 85 %), m.p. 198–200°C. (lit.[27] m.p. 229–230°C).

3.3. Copper Catalysed Cyclization

General Procedure for Cyclizations[23]

The 5-[(phenyl)methylidene]-3-phenylimidazolidine-2,4-diones (2 mmol), copper bronze (0.05 g) and quinoline (5 mL) were refluxed together in a Wood's metal bath and the reaction monitored by TLC for the disappearance of the starting material. Upon completion of the reaction, the mixture was cooled to approximately 150°C, and filtered to remove copper salts. The warm residue was washed with hot EtOH (10 mL) and the filtrate washings combined, evaporated under reduced pressure and diluted with aq. HCl (10 mL, 10%) to give a solid that was subjected to column chromatography on silica gel eluted with (1:1) EtOAc-light petroleum to afford the indoles.

*2-Phenyl-2,3-dihydro-1H-imidazol[1,5-*a*]indole-1,3-dione* (**5**)[28]

Compound **11** (0.50 g, 1.40 mmol) reacted, in a Wood's metal bath at 200°C, within 2 h to give indolo **13** as white needles (0.29 g, 80%), m.p. 198–200°C (lit.[28] m.p. 212–213°C).

*6-Hydroxy-2-phenyl-2,3-dihydro-1H-imidazol[1,5-*a*]indole-1,3-dione* (**6**)

Compound **13** (0.2 g, 0.63 mmol) reacted, in a Wood's metal bath at 180°C, within 1 h to afford **6** as yellow needles (0.16 g, 100 %), m.p. 248–249°C; δ_H (500 MHz, DMSO-d_6) 6.84 (1H, dd, *J* 8.2, 2.0 Hz, 7-H), 7.20 (1H, d, *J* 2.0 Hz, 5-H), 7.34 (1H, s, 8-H), 8.42-7.52 (5H, m, 2′-H to 6′-H), 7.64 (1H, d, *J* 8.2 Hz, 9-H), 10.32 (1H, s, OH), δ_C (500 MHz, DMSO-d_6) 98.5 (C-5), 110.1 (C-9), 114.6 (C-7), 125.1 (C-8a), 125.8 (C-9), 127.2 (C-2′ and C-6′), 127.6 (C-4′), 128.6 (C-3′ and C-5′), 129.1 (C-9a), 131.9 (C1′), 134.2 (C-4a), 148.1 (C-3), 158.2 (C-1), 159.2 (C-6); *m/z*: 279 (M+1, 14%), 278 (M$^+$, 73), 277 (4), 160 (14), 159 (100), 158 (8), 132 (50), 131 (31), 130 (24), 119 (26), 103 (13), 91 (14), 76 (17), 64 (15), 51 (13); (Found: *m/z* 301.05870. $C_{16}H_{10}N_2O_3Na$ requires: *m/z* 301.05835, (M+Na)$^+$).

*6,7-Dimethoxy-2-phenyl-2,3-dihydro-1H-imidazol[1,5-*a*]indole-1,3-dione* (**7**)

Compound **14** (0.5 g, 1.23 mmol) reacted, in a Wood's metal bath at 180°C, within 0.5 h to give indole **7** as yellow needles (0.39 g, 98%), m.p. 244–246°C; δ_H (500 MHz, DMSO-d_6) 4.21 (3H, s, 7-OCH_3), 4.38 (3H, s, 6-OCH_3), 7.25 (1H, s, 5-H), 7.30 (1H, s, 9-H), 7.37 (1H, s, 8-H), 7.43-7.57 (5H, m, 2′-H to 6′-H); δ_C (500 MHz, DMSO-d_6) 56.0 (7-OCH_3), 56.2 (6-OCH_3), 95.6 (C-5), 105.4 (C-9), 109.5 (C-8), 125.0 (C-4a), 127.2 (C-2′ and C-6′), 127.6 (C-8a), 127.8 (C-4′), 128.3 (C-3′ and C-5′), 129.2 (C-3a), 131.8 (C-1′), 147.5 (C-7), 148.0 (C-3), 151.7 (C-6), 158.1 (C-1); *m/z* 324 (M$^+$, absent), 323 (22%), 322 (84), 321 (4), 204 (13), 203 (100), 192 (10), 175 (22), 160 (22), 145 (10), 132 (18), 119 (55), 117 (51), 102 (19), 91 (34), 89 (19), 77 (18), 76 (7), 63 (17), 50 (7); (Found: C, 66.98; H, 4.45; N, 8.50. $C_{18}H_{14}N_2O_{14}$ requires: C, 67.07; H, 4.38; N, 8.69%).

*2-Phenyl-5,6,7-trimethoxy-2,3-dihydro-1-imidazol[1,5-*a*]indole-1,3-dione* (**8**)

Compound **15** (0.5 g, 1.16 mmol) reacted, in a Wood's metal bath at 180°C, within 0.5 h to give indolo **8** as yellow needles, (0.20 g, 50%), m.p. 210–212°C; δ_H (500 MHz, DMSO-d_6) 3.83 (3H, s, 5-OCH_3), 3.85 (3H, s, 6-OCH_3), 3.86 (3H, s, 6-OCH_3), 6.88 (1H, s, 8-H), 7.38 (1H, s, 9-H), 7.47-7.25 (5H, m, 2′-H to 6′-H); δ_C (500 MHz, DMSO-d_6) 56.5 (5-OCH_3), 61.4 (6-OCH_3), 62.8 (7-OCH_3), 101.9 (C-8), 109.4 (C-9), 122.7 (C-4a), 127.8 (C-2′ and C-3′), 128.7 (C-9a), 129.0 (C-4′), 129.2 (C-3′ and C-5′), 130.1 (C-8a), 132.1 (C-1′), 141.0 (C-5), 144.2 (C-6), 146.8 (C-3), 151.8 (C-7), 158.2 (C-1); *m/z* 352 (M$^+$, 44%), 338 (24), 233 (100), 218 (22), 204 (48), 201 (19), 190 (20), 146 (10), 129 (30), 121 (35), 106 (10), 93 (20), 69 (22), 57 (22); (Found: C, 64.60; H, 4.30; N, 7.60. $C_{19}H_{16}N_2O_5$ requires: C, 64.80; H, 4.60; N, 7.90%).

*2-Methyl-2,3-dihydro-1H-imidazol[1,5-*a*]indole-1,3-dione* (**9**)

Compound **18** (0.20 g, 0.084 mmol) reacted, in a Wood's metal bath at 180°C, within 1 h to give **9** as white needles (0.10 g, 75%), m.p. 243–245°C; δ_H (500 MHz, DMSO-d_6) 3.02 (3H, s, CH_3), 7.31(1H, δ, *J* 7.1, 2.0, 1.0 Hz, 7-H), 7.34 (1H, d, *J* 1.0 Hz, 9-H), 7.52 (1H, δ, *J* 7.1, 2.0, 1.0 Hz, 5-H), 7.76 (1H, δ, *J* 7.1, 2.0, 1.0 Hz, 6-H), 7.78 (1H, δ, *J* 7.1, 2.0, 1.0 Hz, 8-H); δ_C (500 MHz, DMSO-d_6) 32.7 (CH_3), 116.1 (C-9), 120.6 (C-5), 131.9 (C-7), 132.5 (C-8), 136.3 (C-6), 137.5 (C-4a), 140.2 (C-8a), 140.4 (C-9a), 149.5 (C-3), 159.3 (C-1). *m/z*: 201 (M+1, 4%), 200 (M$^+$, 39), 144 (6), 143 (96), 116 (5), 115 (100), 100 (4), 89 (4), 88 (20), 62 (12), 56 (8), 50 (5), 43 (4); (Found: C, 66.27; H, 3.96; N, 14.12. $C_{11}H_8N_2O_2$ requires: C, 66.20; H; 4.03; N; 13.99%).

*7-Nitro-2-phenyl-2,3-dihydro-1H-imidazol[1,5-*a*]indole-1,3-dione* (**10**)

Compound **16** (0.500 g, 1.45 mmol), reacted in DMF to afford **10** as gray platelets (0.30 g, 73 %), m.p. 258–260°C; δ_H (500 MHz, DMSO-d_6) 7.28–7.38 (5H, m, 2′-H to 6′-H), 7.67 (1H, s, 9-H), 8.04 (1H, d, *J* 9.0 Hz; 5-H), 8.40 (1H, dd, *J* 9.0, 2.0 Hz, 6-H), 8.82 (1H, d, *J* 2.0 Hz, 8-H); δ_C (500 MHz, DMSO-d_6) 109.3 (C-9), 113.7 (C-5), 121.3 (C-8), 123.6 (C-6), 127.7 (C-2′ and C-6′), 129.1 (C-4′), 129.5 (C-3′ and C-5′), 131.4 (C-9a), 132.0 (C-1′), 132.5 (C-8a), 135.2 (C-4a), 144.2 (C-7), 147.9 (C-3), 158.0 (C-1); *m/z* 308 (M+1, 7%), 307 (M$^+$, 44), 189 (47, 188 (74), 187 (7), 172 (5), 158 (20), 130 (30), 114 (100), 102 (29), 91 (20), 87 (18), 81 (11), 63 (21), 51 (7), 43 (14); (Found: C, 62.19; H, 2.90; N, 13.61. $C_{16}H_9N_3O_4$ requires: C, 62.54, H, 2.95, N, 13.68%).

*8-Bromo-2-phenyl-5,6,7-trimethoxy-2,3-dihydro-1H-imidazol[1,5-*a*] indole-1,3-dione* (**19**)

Compound **15** (0.10 g), CuBr (0.05 g) in dry DMF were refluxed together for 2 h. On cooling, the blue solid was filtered off and the filtrate was poured into H_2O. The aq. phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated off to give a yellow solid that was recrystallized from AcOH to afford **20** as yellow needles (0.09 g, 90%), m.p. 148–150°C; δ_H (500 MHz, DMSO-d_6) 3.85 (3H, s, 6-OCH_3), 3.87 (3H, s, 7-OCH_3), 3.97 (3H, s, 5-OCH_3), 6.94 (1H, s, 9-H), 7.35 (2H, tt, *J* 7.2, 2.0 Hz, 2′-H and 6′-H), 7.45 (1H, tt, *J* 7.2, 2.0 Hz, 4′-H), 7.55 (2H, tt, *J* 7.2, 2.0 Hz, 3′-H and 5′-H), δ_C (500 MHz, DMSO-d_6) 56.7 (6-OCH_3), 61.5 (7-OCH_3), 62.9 (5-OCH_3), 93.4 (C-8), 99.1 (C-9), 119.6 (C-9a), 127.8 (C-2′ and C-6′), 128.2 (C-8a), 128.8 (C-4′), 129.3 (C-3′ and C-5′), 131.8 (C-1′), 141.1 (C-7), 145.0 (C-6), 144.5 (C-4a), 146.1 (C-3), 151.5 (C-5), 152.5 (C-1); *m/z* 433 (M(^{81}Br)+1, 8%), 432 (M(^{81}Br)$^+$, 39), 431 M(^{79}Br)+1, 8), 430 M(^{79}Br)$^+$, 39), 386 (6), 368 (8), 314 (12), 313 (100), 311 (99), 310 (13), 296 (13), 282 (37), 267 (18), 255 (10), 238 (17), 224 (13), 210

(7), 182 (7), 161 (7), 146 (16), 131 (9), 119 (38), 114 (17), 91 (29), 83 (19), 69 (11), 55 (11), 43 (11); (Found: C, 52.99; H, 3.32; N, 6.64. $C_{19}H_{115}BrN_2O_5$ requires: C, 52.92; H, 3.51; N, 6.50%).

3.4 Radical Promoted Cyclization of 11, 12 and 14

General Procedure for Radical Cyclization[29]

Bu_3SnH (1.5 mol. equiv of 97%) was added dropwise by syringe to the solution of the imidazolidine-2,4-dione and AIBN (0.05 g) in dry $PhCH_3$ (5 mL) under argon and the mixture heated at reflux. The reactions were monitored by TLC. Upon completion the solutions were poured into aq. KF solution (50%, 50 mL) and stirred at r.t. overnight. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were further washed with aq. NaOH and dried over $MgSO_4$. Excess solvent was removed under reduced pressure and the residue subjected to column chromatography on silica gel eluted with (1:1) EtOAc-light petroleum to afford the respective indoles. Derivatives **11** and **12** reacted, after 3 h, to afford **5** as white crystals (99, 68%, respectively), while derivative **14** (1.00 g, 2.90 mmol) reacted, after 3 h, to afford **7** (89%).

5,5-Dibutyl-6,7,8-trimethoxy-2-phenyl-1,2,3,5-tetrahydroimidazo-5-stanna-[1,5-b]isoquinoline-1,3-dione (**20**)

Compound **15** (1.50 g, 3.50 mmol) reacted to afford, after 3 h, **20** as white needles (1.50 g, 77%), m.p. 98–100°C; δ_H (500 MHz, DMSO-d_6) 0.80 (6H, t, *J* 7.5 Hz, 4″-CH_3), 1.29 (4H, m, 3″-CH_2), 1.57 (4H, m, 1″-CH_2), 1.48 (4H, br m, 2″-CH_2), 3.78 (3H, s, 7-OCH_3), 3.83 (3H, s, 8-OCH_3), 3.92 (3H, s, 6-OCH_3), 6.53 (1H, s, 4-H), 7.21 (1H, t, J_{Sn} 18.0 Hz, 9-H), 7.40, (1H, tm, *J* 7.2 Hz, 4′-H), 7.46 (2H, tm *J* 7.2 Hz, 2′-H and 6′-H), 7.48 (2H, tm, *J* 7.2 Hz, 3′-H and 5′-H); δ_C (500 MHz, DMSO-d_6) 13.7 (C-4″), 16.0 (C-3″), 26.0 (t, J_{Sn} 69.0 Hz, C-2″), 27.7 (t, J_{Sn} 22.6 Hz, C-1″), 56.5 (8-OCH_3), 60.8 (6-OCH_3), 61.3 (7-OCH_3), 110.2 (C-4), 113.0 (C-9), 121.6 (C-6a), 126.4 (C-2′ and C-6′), 128.0 (C-4′), 129.2 (C-3′ and C-5′), 132.3 (C-3a), 132.8 (C-1′), 135.5 (C-4a), 140.0 (C-7), 155.2 (C-6), 155.7 (C-8), 158.2 (C-1), 165.1 (C-3); *m/z* 586 (M+2, 3%), 584 (M^+, 1), 582 (3), 529 (6), 473 (5), 457 (3), 308 (2), 280 (2), 120 (3), 119 (9), 91 (10), 81 (10), 69 (43), 57 (77), 55 (30), 41 (100); (Found: C, 55.58; H, 5.88; N, 4.82. $C_{27}H_{34}N_2O_5Sn$ requires: C, 55.51; H, 5.69; N, 4.79%).

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