Highly Efficient Aluminum Trichloride Catalyzed Michael Addition of Indoles and Pyrroles to Maleimides

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Abstract: A highly efficient synthetic strategy for Michael addition of indoles and pyrroles to maleimides has been developed using the Lewis acids zinc chloride or aluminum trichloride as the catalyst. The reactions generated 3-substituted indoles and 2-substituted pyrroles in high yields with excellent regioselectivity in the presence of a catalytic amount of zinc chloride or aluminum trichloride under mild reaction conditions. The method is simple, efficient, and practical.

Key words: Michael addition, indole, pyrrole, maleimide, aluminum trichloride

Indole derivatives are ubiquitous structural features of many alkaloid natural products and drug candidates.[1] Among them, indolylsuccinimide rings are important building blocks in the synthesis of biologically active compounds and natural products.[2] Their derivatives are important intermediates in organic synthesis and pharmaceutical chemistry.[3]

Generally, indolylsuccinimides are prepared by the reaction of indoles with maleimides in acetic acid. However, the reaction requires long reaction times, and the products are obtained in low yields. [4] The acid-catalyzed conjugate addition of indoles requires careful control of the acidity to prevent side reactions such as dimerization or polymerization.[5] Recently, Michael addition and Friedel–Crafts-type alkylation of heteroaromatics with electron-deficient α,β-unsaturated carbonyl compounds have been used as powerful methods for direct C–C bond formation in the functionalization of these biologically important motifs.[6] The 3-position of indole is the preferred site for electrophilic substitution reactions, and the resultant 3-alkyl- or 3-acylindoles are versatile intermediates for the synthesis of a wide range of indole derivatives. A simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of Lewis acids such as $InBr_3$,[7] $CeCl_3$–NaI,[8] $Zn(OTf)_2$,[9] $ZrCl_4$,[10] Au(III),[11] Ru(III),[12] $Zn(OAc)_2$,[13] Al-MCM-14,[14] $Bi(NO_3)_3$,[15] or I_2,[16] which have been exploited with varying degrees of success. However, the reaction usually demands high catalyst loadings (>10 mol%), long reaction times ranging from several hours to several days in some cases, strong acidic conditions, expensive and hazardous reagents, and special reaction conditions to enhance reactivity such as heating, microwave irradiation,[17] or ionic liquids.[18] The majority of these reactions were studied using highly nucleophilic indoles, and even electron-poor indoles sometimes give unsatisfactory yields. Thus, an efficient, economical and environmentally benign Lewis acid catalyst is highly desirable for this process.

Recently, there has been an increase in the use of aluminum trichloride in chemistry that has seen it emerged as a safe, economical, air and moisture tolerant, alternative Lewis acid in various organic transformations.[19] In continuation of our efforts to develop selective, efficient, and mild synthetic methodologies for the preparation of heterocycle derivatives, herein, we report the aluminum trichloride catalyzed Michael addition of biologically and chemically important indoles and pyrroles to maleimides. In addition, the notable advantages of this methodology are mild conditions, short reaction times, high yields, and no side reaction products.

In the initial studies, we chose 1*H*-indole (**1**) as a model compound to study this reaction, because the product, 3-indolylsuccinimide **3a**, is solid and easy to purify. As shown in Table 1, the reaction between 1*H*-indole (**1**) and maleimide (**2**) in the presence of Lewis acid is accomplished by heating the reagents in 1,2-dichloroethane at reflux for eight hours. Since, Lewis acid catalyzed addition of indole to maleimide has not previously been reported in the literature, zinc triflate was initially chosen as the catalyst. Unfortunately, zinc triflate and yttrium triflate do not function as catalysts in this reaction (entries 1 and 2) and the starting materials were recovered. Using bismuth nitrate as the catalyst gave numerous products because of its oxidative properties (entry 3). Next, we examined the use of classic Lewis acids, such as $ZnCl_2$, $ZnBr_2$, $Zn(OAc)_2$, $FeCl_3$, and $AlCl_3$. Zinc chloride was an effective catalyst (entry 4); 3-indolylsuccinimide **3a** was formed in 88% yield in the presence of 0.1 equivalents of zinc chloride. In contrast, using 0.1 equivalents of iron(III) chloride gave 3-indolylsuccinimide **3a** in 53% yield (entry 7). Compound **3a** was also obtained in 80% yield using aluminum trichloride as catalyst. The possible reason is that iron(III) chloride lead to the partial polymerization of maleimide due to its oxidation. Using zinc chloride as the catalyst, the solvent was varied (entries 4 and 10–13); 3-indolylsuccinimide **3a** was not formed using *N*,*N*-dimethylformamide, tetrahydrofuran, or dioxane as the solvent. These results demonstrate that zinc chlo-

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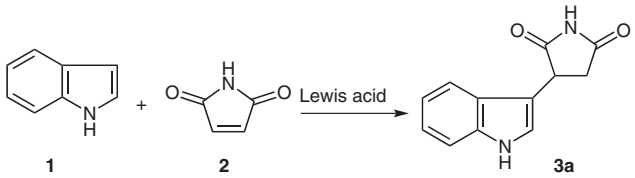
ride is a more effective catalyst than iron(III) chloride. It should be noted that without any catalyst, the reaction did not generate the desired product **3a** (entry 9).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	$Zn(OTf)_2$	DCE	24	0
2	$Y(OTf)_3$	DCE	24	0
3	$Bi(NO_3)_3$	DCE	8	0
4	$ZnCl_2$	DCE	8	88
5	$ZnBr_2$	DCE	8	85
6	$Zn(OAc)_2$	DCE	24	45
7	$FeCl_3$	DCE	8	53
8	$AlCl_3$	DCE	8	80
9	no catalyst	DCE	24	0
10	$ZnCl_2$	DMF[c]	24	0
11	$ZnCl_2$	THF	24	0
12	$ZnCl_2$	dioxane	24	0
13	$ZnCl_2$	$CHCl_3$	24	38

[a] Reaction conditions: 1*H*-indole (**1**, 10 mmol), maleimide (**2**, 10 mmol), catalyst (10 mol%), solvent (50 mL), reflux, stirring.
[b] Isolated yield.
[c] Reaction temperature ~100–105 °C.

With a catalytic amount of zinc chloride (≤10 mol% based on indole), 1*H*-indole (**1**) reacted with maleimide (**2**) to give 3-indolylsuccinimide **3a** (Figure 1). As shown in Figure 1, increasing the loading of zinc chloride initially led to a sharp increase in the yield and then it plateaued. Using 20 mol% of zinc chloride as the catalyst gave a ~95% yield.

To further illustrate the utility of this method, a series of substrates including indoles and pyrroles were used as substrates. The results are summarized in Table 2. In some cases, isolated yields were good and ranged from 82 to 95%. However, the methodology is unsuitable for the Michael addition of electron-deficient indoles (5-nitro-1*H*-indole and 5-bromo-1*H*-indole) to maleimides; using zinc chloride as a catalyst under the optimized conditions did not give the Michael product. Using chlorobenzene, a high-boiling solvent, in the procedure instead of 1,2-dichloroethane in order to elevate the reaction temperature

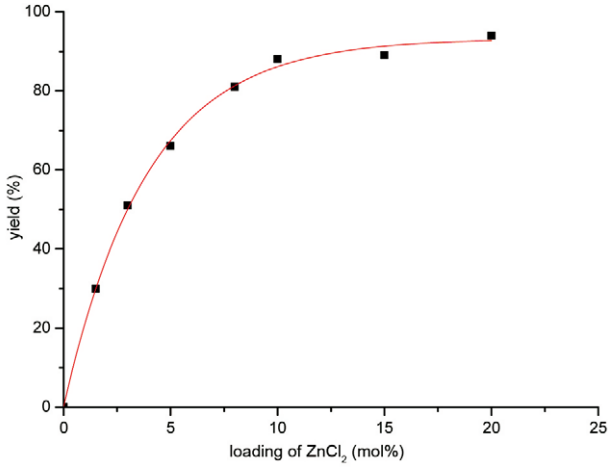


Figure 1 Effect of catalyst loading on yield. *Reaction conditions*: indole (**1**, 3 mmol), maleimide (**2**, 3 mmol), 1,2-dichloroethane (15 mL), reflux, 8 h.

also was unsuccessful due to polymerization of the maleimides. Next, we examined the use of aluminum trichloride as the Lewis acid. The results suggest aluminum trichloride is an efficient catalyst for the addition of electron-deficient indoles to maleimides (entries 9–12); 3-indolylsuccinimides **3i–l** were obtained ca. 90% yield.

Crystals of compound **3b** suitable for X-ray analysis was obtained by slow evaporation of a solution of this compound in a mixture of ethyl acetate and ethanol (1:1). The crystal data suggested that the reaction was clean and gave the C3-substitution product exclusively (Figure 2). No C1-substitution product was isolated. Using pyrrole as substrate, only C2-substitution products **3m**,**n** were obtained in ca. 90% yield. The packing view of **3b** in the unit cell and tables of X-ray crystallographic data can be found in the Supporting Information. The target compounds **3a–l** were obtained in good to excellent yields with no formation of side products, such as polymers, that are frequently encountered under the influence of strong protic acids.

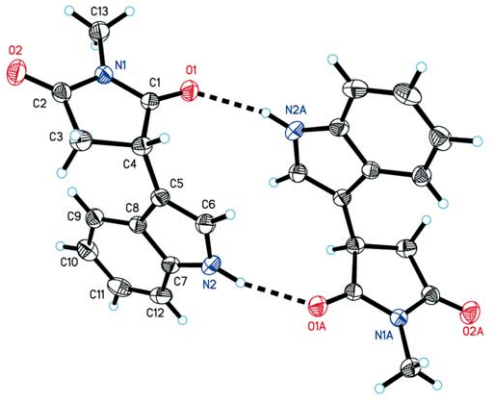


Figure 2 ORTEP structure of the compound **3b**, showing 50% probability ellipsoids

Table 2 Lewis Acid Catalyzed Michael Addition of Indoles and Pyrroles to Maleimides[a]

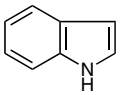
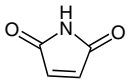
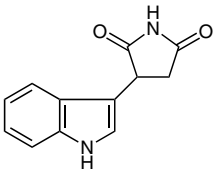
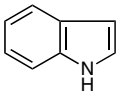
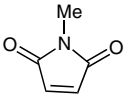
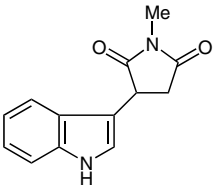
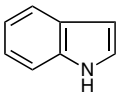
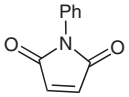
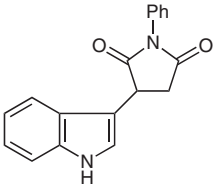
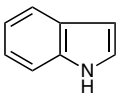
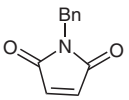
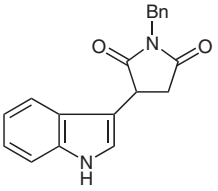
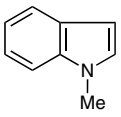
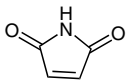
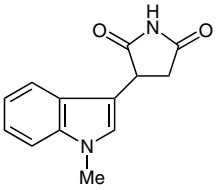
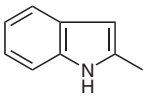
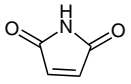
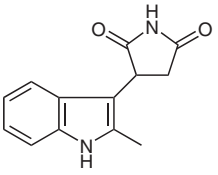
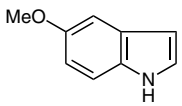
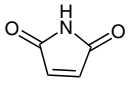
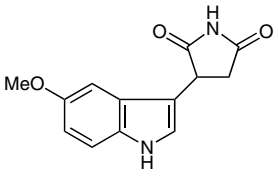
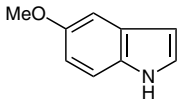
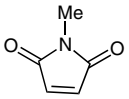
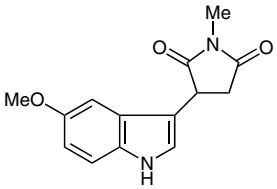
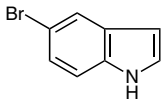
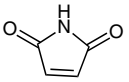
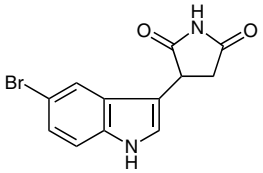
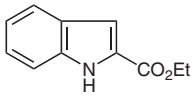
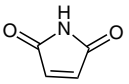
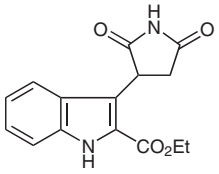
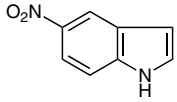
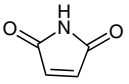
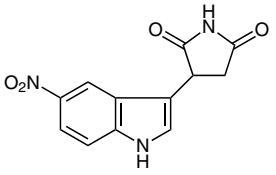
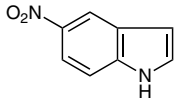
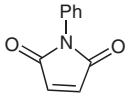
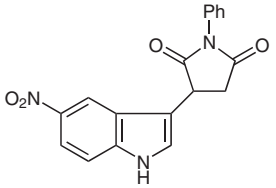
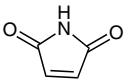
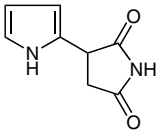
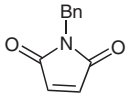
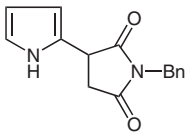
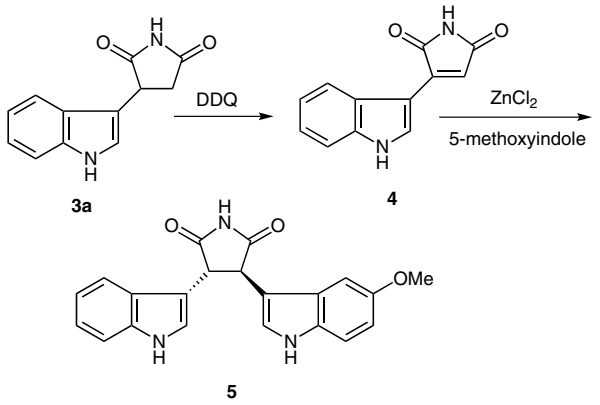
Entry	Indole	Maleimide	Catalyst	Time (h)	Product	Yield[b] (%)
1			$ZnCl_2$	8	 **3a**	88
2			$ZnCl_2$	8	 **3b**	90
3			$ZnCl_2$	8	 **3c**	92
4			$ZnCl_2$	8	 **3d**	91
5			$ZnCl_2$	8	 **3e**	95
6			$ZnCl_2$	8	 **3f**	89
7			$ZnCl_2$	8	 **3g**	95

Table 2 Lewis Acid Catalyzed Michael Addition of Indoles and Pyrroles to Maleimides[a] (continued)

Entry	Indole	Maleimide	Catalyst	Time (h)	Product	Yield[b] (%)
8			$ZnCl_2$	8	 **3h**	90
9			$AlCl_3$	12	 **3i**	85
10			$AlCl_3$	12	 **3j**	82
11			$AlCl_3$	16	 **3k**	86
12			$AlCl_3$	16	 **3l**	89
13			$ZnCl_2$	8	 **3m**	92
14			$ZnCl_2$	8	 **3n**	96

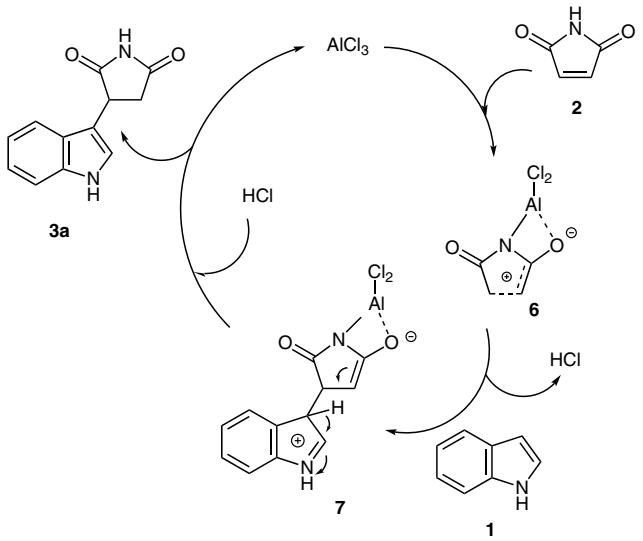
[a] Reaction conditions: indole (10 mmol), maleimide (10 mmol), Lewis acid (1 mmol), reflux.
[b] Isolated yield.

With the compound **3a** in hand, it was oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to provide 3-indolylmaleimide **4**.[4a] Then, compound **4** was subjected to Michael addition with 5-methoxy-1*H*-indole in the presence of zinc chloride to give *trans*-bisindolylsuccinimide **5** in 90% yield (Scheme 1). This *trans* stereochemistry was deduced from the existence of the signal of succinimide methine protons at δ = 3.52.[3d,20] It provided a useful intermediate for the synthesis of indolylmaleimides with heteroaromatic moieties.



Scheme 1

We believe that aluminum trichloride functions as a catalyst in our Michael addition protocol for both electron-donating and electron-deficient indoles. A plausible mechanism for 3-indolylmaleimide compounds is proposed in Scheme 2. Although we do not have additional evidence for this, we hypothesized that aluminum trichloride readily coordinates to the oxygen and nitrogen atoms of maleimide.[21] Rapid formation of **7** may be due to the initial formation of intermediate **6** from aluminum trichloride and maleimide, which presumably reduces the activation energy required for Michael addition. Next, indole is added to labile intermediate **6** to yield the corresponding Michael adduct **7**, which upon subsequent electron reorganization followed by hydrogen transfer yields compound **3a**, releasing the catalyst for next cycle. In the catalytic cycle, it is thought that aluminum trichloride promotes the reaction by increasing the electrophilic character of the enal. A mechanistic study in our laboratory to clarify the pathways for aluminum trichloride employing Michael addition is under way.



Scheme 2 Proposed catalytic cycle for the reaction of indole and maleimide catalyzed by aluminum trichloride

In summary, aluminum trichloride and zinc chloride have been demonstrated to be a highly selective and efficient catalyst for the Michael addition of a variety of indoles and pyrroles to N-substituted maleimides. The reactions were performed smoothly to generate the desired products 3-substituted indolylsuccinimides in good yields under safe experimental conditions. The notable advantages of this methodology are mild conditions, short reaction times, high yields, and the absence of side products. This method offers one of the important motifs for synthesis of 3-substituted indoles, as natural products, biologically active compounds, and pharmaceutical agents.

Melting points were determined with RY-1 apparatus and are uncorrected. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV 400 MHz spectrometer in DMSO-d_6 and $CDCl_3$ with TMS as internal standard. EI mass spectra were recorded on Shimadzu QP-2010 GC-MS system and Waters Micromass GCT system. Maleimides were purchase from TCI China. All chemicals and reagents were purchased from known commercial suppliers and used without further purification. Mp and ^{1}H NMR data of known compounds is in accord with that reported in the literature. The purity of substrates and the monitoring of reactions were performed by TLC on silica gel polygram SILG/UV 254 plates.

Crystals of 3-(1*H*-indole-3-yl)-1-methylpyrrolidine-2,5-dione (**3b**) were obtained by dissolving **3b** (0.2 g) in EtOAc (3 mL) and EtOH (3 mL) and evaporating the solvent slowly at r.t. over 2 d. The data were collected on CAD-4 diffractometer equipped with graphite-monochromatic MoKα radiation (λ = 0.71037 Å) by using an ω scan mode at 293(2) K. The structure of **3b** is shown in Figure 2. X-ray crystallographic data for compound **3b** can be found in the Supporting Information.

Michael Addition of Indoles to Maleimides Catalyzed by Zinc Chloride; General Procedure

A mixture of the indole (10 mmol), maleimide (10 mmol), and anhyd $ZnCl_2$ (1 mmol) in 1,2-dichloroethane (40 mL) was stirred and refluxed for the specified time (TLC monitoring). After completion of the reaction, the mixture was cooled to r.t., and H_2O (15 mL) was added. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with H_2O (2 × 10 mL), and dried (Na_2SO_4). The solvent was removed and the residue was recrystallized (EtOH) to yield the product. For compounds **3i–l**, anhyd $AlCl_3$ was used instead of anhyd $ZnCl_2$. The mp and ^{1}H NMR data of known products are in accord with that reported in the literature.

3-(1*H*-Indole-3-yl)pyrrolidine-2,5-dione (3a)[4a]

White crystalline solid; yield: 1.88 g (88%); mp 192–194 °C.

IR (KBr): 3425, 3139, 3056, 2782, 1770, 1707, 1554, 1456, 743 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.76 (dd, *J* = 18.0, 5.6 Hz, 1 H, CH_2), 3.18 (dd, *J* = 18.0, 9.5 Hz, 1 H, CH_2), 4.34 (dd, *J* = 9.5, 4.7

Hz, 1 H, CH), 7.00 (t, J = 7.2 Hz, 1 H, H_{Ar}), 7.10 (t, J = 7.0 Hz, 1 H, H_{Ar}), 7.32 (s, 1 H, H_{Ar}), 7.37 (d, J = 7.8 Hz, 1 H, H_{Ar}), 7.42 (d, J = 7.7 Hz, 1 H, H_{Ar}), 11.01 (s, 1 H, NH), 11.28 (s, 1 H, NH).

MS (EI): m/z = 214 $[M]^+$, 162, 156, 143, 115, 105, 89.

3-(1*H*-Indole-3-yl)-1-methylpyrrolidine-2,5-dione (3b)[4a,22]
White crystalline solid; yield: 2.06 g (90%); mp 170–172 °C.

IR (KBr): 3467, 3332, 2936, 1765, 1682, 1557, 1443, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.79 (dd, J = 18.1, 5.4 Hz, 1 H, CH_2), 2.92 (s, 3 H, CH_3), 3.23 (dd, J = 17.8, 9.2 Hz, 1 H, CH_2), 4.35 (dd, J = 9.2, 5.4 Hz, 1 H, CH), 7.00 (d, J = 7.0 Hz, 1 H, H_{Ar}), 7.08 (d, J = 7.1 Hz, 1 H, H_{Ar}), 7.33 (s, 1 H, H_{Ar}), 7.38 (br s, 2 H, H_{Ar}), 11.02 (s, 1 H, NH).

MS (EI): m/z = 228 $[M]^+$, 199, 170, 162, 143, 115, 89.

3-(1*H*-Indole-3-yl)-1-phenylpyrrolidine-2,5-dione (3c)[23]
White crystalline solid; yield: 2.67 g (92%); mp 149–151 °C.

IR (KBr): 3402, 3344, 3053, 2866, 1778, 1704, 1555, 1495, 745 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.97 (dd, J = 18.1, 5.4 Hz, 1 H, CH_2), 3.41 (dd, J = 18.1, 9.6 Hz, 1 H, CH_2), 4.55 (d, J = 9.6, 4.2 Hz, 1 H, CH), 7.03 (d, J = 9.6 Hz, 1 H, H_{Ar}), 7.13 (t, J = 13.4 Hz, 1 H, H_{Ar}), 7.35 (d, J = 6.7 Hz, 2 H, H_{Ar}), 7.41–7.44 (m, 3 H, H_{Ar}), 7.50–7.52 (m, 3 H, H_{Ar}), 11.08 (s, 1 H, NH).

MS (EI): m/z = 290 $[M]^+$, 219, 173, 162, 143, 129, 117, 90.

1-Benzyl-3-(1*H*-indole-3-yl)pyrrolidine-2,5-dione (3d)
White crystalline solid; yield: 2.76 g (91%); mp 119–122 °C.

IR (KBr): 3442, 3326, 3037, 2937, 1769, 1698, 1588, 1493, 744 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.86 (d, J = 17.7 Hz, 1 H, CH_2), 3.33 (dd, 1 H, CH_2), 4.44 (d, J = 17.7 Hz, 1 H, CH), 4.65 (s, 2 H, CH_2), 6.91 (d, J = 6.5 Hz, 1 H, H_{Ar}), 7.08 (s, 1 H, H_{Ar}), 7.18–7.55 (m, 8 H, H_{Ar}), 11.03 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.3, 38.1, 42.1, 111.1, 112.1, 118.8, 119.1, 121.8, 123.9, 126.2, 127.9, 128.2, 128.9, 136.7, 136.9, 176.9, 178.9.

MS (EI): m/z = 304 $[M]^+$, 213, 206, 187, 171, 143, 115, 89.

HRMS (EI): m/z $[M]^+$ calcd for $C_{19}H_{16}N_2O_2$: 304.1212; found: 304.1210.

3-(1-Methyl-1*H*-indole-3-yl)pyrrolidine-2,5-dione (3e)[24]
White crystalline solid; yield: 2.17 g (95%); mp 139–141 °C.

IR (KBr): 3265, 3069, 2936, 1775, 1712, 1616, 1544, 1517, 1475, 737 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.72 (dd, J = 18.0, 4.6 Hz, 1 H, CH_2), 3.19 (dd, J = 18.0, 9.6 Hz, 1 H, CH_2), 3.74 (s, 3 H, CH_3), 4.35–4.31 (m, 1 H, CH), 7.04 (t, J = 7.2 Hz, 1 H, H_{Ar}), 7.17 (t, J = 7.4 Hz, 1 H, H_{Ar}), 7.31 (s, 1 H, H_{Ar}), 7.43 (t, J = 6.7 Hz, 2 H, H_{Ar}), 11.31 (s, 1 H, NH).

MS (EI): m/z = 228 $[M]^+$, 199, 179, 157, 142, 130, 115, 89.

3-(2-Methyl-1*H*-indole-3-yl)pyrrolidine-2,5-dione (3f)[4b]
White crystalline solid; yield: 2.03 g (89%); mp 230–232 °C.

IR (KBr): 3364, 3189, 3062, 2921, 1771, 1706, 1497, 1457, 741 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.32 (s, 3 H, CH_3), 2.64 (dd, J = 18.1, 4.2 Hz, 1 H, CH_2), 3.13 (dd, J = 18.1, 9.8 Hz, 1 H, CH_2), 4.32 (dd, J = 8.3, 4.2 Hz, 1 H, CH), 6.93 (d, J = 7.2 Hz, 1 H, H_{Ar}), 7.01 (t, J = 7.3 Hz, 1 H, H_{Ar}), 7.12 (d, J = 7.7 Hz, 1 H, H_{Ar}), 7.27–7.29 (m, 1 H, H_{Ar}), 10.94 (s, 1 H, NH), 11.40 (s, 1 H, NH).

MS (EI): m/z = 228 $[M]^+$, 213, 183, 157, 130, 115, 89.

3-(5-Methoxy-1*H*-indole-3-yl)pyrrolidine-2,5-dione (3g)[22,25]
White crystalline solid; yield: 2.31 g (95%); mp 206–209 °C.

IR (KBr): 3349, 3191, 3072, 2943, 1777, 1690, 1583, 1486, 804 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.75 (dd, J = 18.1, 4.0 Hz, 1 H, CH_2), 3.18 (dd, J = 17.6, 9.4 Hz, 1 H, CH_2), 3.74 (s, 3 H, CH_3), 4.30 (s, 1 H, CH), 6.76 (d, J = 8.2 Hz, 1 H, H_{Ar}), 6.91 (s, 1 H, H_{Ar}), 7.25–7.27 (m, 2 H, H_{Ar}), 10.88 (s, 1 H, NH), 11.29 (s, 1 H, NH).

MS (EI): m/z = 244 $[M]^+$, 228, 202, 173, 147, 132, 104, 97, 89.

3-(5-Methoxy-1*H*-indole-3-yl)-1-methylpyrrolidine-2,5-dione (3h)[22]
White crystalline solid; yield: 2.32 g (90%); mp 138–140 °C.

IR (KBr): 3360, 3126, 3024, 2968, 2938, 1770, 1698, 1578, 1457, 867, 840 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.78 (dd, J = 18.0, 3.4 Hz, 1 H, CH_2), 2.92 (s, 3 H, CH_3), 3.23 (dd, J = 17.9, 9.3 Hz, 1 H, CH_2), 3.73 (s, 3 H, CH_3), 4.32 (dd, J = 9.3, 6.6 Hz, 1 H, CH), 6.76 (d, J = 8.7 Hz, 1 H, H_{Ar}), 6.87 (s, 1 H, H_{Ar}), 7.25–7.27 (m, 2 H, H_{Ar}), 10.88 (s, 1 H, NH).

MS (EI): m/z = 258 $[M]^+$, 243, 173, 158, 130, 115, 89.

3-(5-Bromo-1*H*-indole-3-yl)pyrrolidine-2,5-dione (3i)[4a,22]
White crystalline solid; yield: 2.48 g (85%); mp 210–213 °C.

IR (KBr): 3347, 3053, 2927, 1769, 1706, 1558, 1460, 877, 801 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.82 (dd, J = 17.9, 4.7 Hz, 1 H, CH_2), 3.18 (dd, J = 18.0, 9.4 Hz, 1 H, CH_2), 4.35 (dd, J = 9.3, 6.6 Hz, 1 H, CH), 7.22 (d, J = 8.5 Hz, 1 H, H_{Ar}), 7.35 (d, J = 8.6 Hz, 1 H, H_{Ar}), 7.41 (s, 1 H, H_{Ar}), 7.65 (s, 1 H, H_{Ar}), 11.26 (s, 1 H, NH), 11.30 (s, 1 H, NH).

MS (EI): m/z = 292, 294 $[M]^+$, 221, 223, 195, 171, 143, 115, 88.

Ethyl 3-(2,5-Dioxopyrrolidin-3-yl)-1*H*-indole-2-carboxylate (3j)
White crystalline solid; yield: 2.34 g (82%); mp 102–104 °C.

IR (KBr): 3563, 3472, 3316, 3054, 2984, 1764, 1701, 1568, 1441, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.36–1.30 (m, 3 H, CH_3), 2.70 (dd, J = 17.6, 6.1 Hz, 1 H, CH_2), 3.11 (dd, J = 17.6, 9.6 Hz, 1 H, CH_2), 4.31 (q, J = 12.0 Hz, 2 H, CH_2), 4.90 (dd, J = 9.3, 6.6 Hz, 1 H, CH), 7.12 (dd, J = 14.3, 7.0 Hz, 1 H, H_{Ar}), 7.30 (t, J = 7.6 Hz, 1 H, H_{Ar}), 7.48 (d, J = 8.0 Hz, 1 H, H_{Ar}), 7.64 (d, J = 7.7 Hz, 1 H, H_{Ar}), 11.32 (s, 1 H, NH), 11.87 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 14.6, 38.3, 38.6, 61.0, 113.2, 118.7, 120.1, 120.5, 123.8, 125.6, 127.6, 136.4, 161.6, 178.3, 180.1.

MS (EI): m/z = 286 $[M]^+$, 240, 213, 189, 169, 143, 115, 89.

HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{14}N_2O_4$: 286.0954; found: 286.0950.

3-(5-Nitro-1*H*-indole-3-yl)pyrrolidine-2,5-dione (3k)
White crystalline solid; yield: 2.45 g (86%); mp 224–226 °C.

IR (KBr): 3396, 3073, 1775, 1705, 1518, 1468, 817 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.97 (dd, J = 18.0, 5.1 Hz, 1 H, CH_2), 3.25 (dd, J = 7.9, 9.4 Hz, 1 H, CH_2), 4.58 (dd, J = 9.3, 6.6 Hz, 1 H, CH), 7.60 (d, J = 9.0 Hz, 1 H, H_{Ar}), 7.70 (s, 1 H, H_{Ar}), 8.07 (d, J = 9.0 Hz, 1 H, H_{Ar}), 8.59 (s, 1 H, H_{Ar}), 11.41 (s, 1 H, NH), 11.86 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 37.2, 38.9, 112.6, 114.3, 116.7, 117.2, 126.2, 127.4, 140.0, 140.9, 178.3, 179.9.

MS (EI): m/z = 259 $[M]^+$, 229, 188, 158, 142, 115, 89.

HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_9N_3O_4$: 259.0593; found: 259.0596.

3-(5-Nitro-1*H*-indole-3-yl)-1-phenylpyrrolidine-2,5-dione (3l)
White crystalline solid; yield: 2.98 g (89%); mp 106–109 °C.

IR (KBr): 3396, 3073, 1775, 1705, 1518, 1468, 900, 817 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.15 (dd, J = 18.0, 5.1 Hz, 1 H, CH_2), 3.45 (dd, J = 17.9, 9.4 Hz, 1 H, CH_2), 4.75 (m, 1 H, CH), 7.36–7.53 (m, 6 H, H_{Ar}), 7.77 (s, 1 H, H_{Ar}), 8.03 (d, J = 9.0 Hz, 1 H, H_{Ar}), 8.63 (s, 1 H, H_{Ar}), 11.91 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.3, 37.9, 112.6, 114.1, 116.7, 117.3, 126.2, 127.6, 127.7, 128.8, 129.4, 133.0, 140.0, 141.0, 175.9, 177.5.

MS (EI): m/z = 335, 215, 207, 188, 142, 115, 89.

HRMS (EI): m/z $[M]^+$ calcd for $C_{18}H_{13}N_3O_4$: 335.0906; found: 335.0907.

3-(1*H*-Pyrrole-2-yl)pyrrolidine-2,5-dione (3m)
White crystalline solid; yield: 1.50 g (92%); mp 86–88 °C.

IR (KBr): 3403, 3315, 3083, 2883, 1784, 1696, 1537, 730 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.67 (dd, J = 17.9, 6.0 Hz, 1 H, CH_2), 3.04 (dd, J = 17.8, 9.5 Hz, 1 H, CH_2), 4.09 (br s, 1 H, CH), 5.92 (br s, 2 H, H_{Ar}), 6.66 (s, 1 H, H_{Ar}), 10.79 (s, 1 H, NH), 11.17 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 37.3, 40.9, 106.2, 107.7, 118.2, 127.2, 178.1, 179.1.

MS (EI): m/z = 164 $[M]^+$, 135, 119, 105, 93.

HRMS (EI): m/z $[M]^+$ calcd for $C_8H_8N_2O_2$:164.0586; found: 164.0587.

1-Benzyl-3-(1*H*-pyrrole-2-yl)pyrrolidine-2,5-dione (3n)
White crystalline solid; yield: 2.43 g (96%); mp 152–154 °C.

IR (KBr): 3302, 3138, 2950, 1766, 1686, 1528, 740, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.84 (dd, J = 18.0, 5.6 Hz, 1 H, CH_2), 3.18 (dd, J = 17.9, 9.4 Hz, 1 H, CH_2), 4.22 (s, 1 H, CH), 4.58 (br s, 2 H, CH_2), 5.93 (s, 2 H, H_{Ar}), 6.69 (s, 1 H, H_{Ar}), 7.27–7.32 (m, 5 H, H_{Ar}), 10.85 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 36.0, 39.6, 42.0, 106.3, 107.8, 118.4, 126.8, 127.8, 127.9, 128.9, 136.6, 176.5, 177.43.

MS (EI): m/z = 254 $[M]^+$, 187, 163, 132, 121, 93.

HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{14}N_2O_2$: 254.1055; found: 254.1060.

3-(1*H*-Indole-3-yl)-1*H*-pyrrole-2,5-dione (4)
A soln of DDQ (456 mg, 2 mmol) in dioxane (20 mL) was slowly added to a soln of **3a** (428 mg, 2 mmol) in dioxane (20 mL). The mixture was stirred at r.t. for 12 h. After filtration and removal of the solvent, the residue was dissolved in *i*-PrOH (20 mL). The precipitate was filtered off, and the solid was washed with *i*-PrOH before purification by flash chromatography (EtOAc–cyclohexane, 3:7) to give **4** (350 mg, 82%) as a red crystalline solid; mp 224–226 °C. This compound was reported in literature.[2a,4a] All spectral data matched previously reported data.

IR (KBr): 3433, 3347, 3240, 3057, 1751, 1702, 1601, 740 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.78 (s, 1 H, H_{Ar}), 7.23 (dd, J = 13.4, 8.4 Hz, 2 H, H_{Ar}), 7.52 (d, J = 7.5 Hz, 1 H, H_{Ar}), 7.96 (d, J = 7.4 Hz, 1 H, H_{Ar}), 8.36 (s, 1 H, H_{Ar}), 10.73 (s, 1 H, NH), 12.00 (s, 1 H, NH).

MS (EI): m/z = 212 $[M]^+$, 184, 156, 141, 128, 122, 114.

***trans*-3-(1*H*-Indole-3-yl)-4-(5-methoxy-1*H*-indole-3-yl)pyrrolidine-2,5-dione (5)**
White crystalline solid; yield: 0.45 g (90%); mp 150–152 °C.

IR (KBr): 3401, 3066, 2943, 1774, 1712, 1581, 1481, 749, 802 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.52 (d, J = 16.2 Hz, 2 H, 2 CH), 3.60 (s, 3 H, CH_3), 6.70–6.75 (m, 2 H, H_{Ar}), 6.87 (s, 1 H, H_{Ar}), 7.04 (s, 1 H, H_{Ar}), 7.18–7.25 (m, 2 H, H_{Ar}), 7.30–7.32 (m, 2 H, H_{Ar}), 7.36 (d, J = 7.6 Hz, 1 H, H_{Ar}), 10.86 (s, 1 H, NH), 11.01 (s, 1 H, NH), 11.41 (s, 1 H, NH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 55.7, 60.2, 102.8, 111.2, 112.2, 112.7, 114.9, 115.3, 119.0, 120.2, 121.5, 123.8, 124.3, 125.8, 126.2, 132.7, 137.4, 153.1, 177.4, 180.4.

MS (EI): m/z = 359 $[M]^+$, 329, 318, 288, 258, 243, 214, 173, 137, 128, 115, 109.

HRMS (EI): m/z $[M]^+$ calcd for $C_{21}H_{17}N_3O_3$:359.1270; found: 359.1273.

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