Expedited microwave-assisted *N*-alkylation of isatins utilizing DBU

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Abstract

The *N*-alkylation of a variety of isatins with alkyl or benzylic halides can be effected under microwave irradiation in ethanol using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. The conditions employed allow for the expedited synthesis of such substrates wherein the products precipitate from the reaction mixture in high yields and high purity after simple filtration. As will be described, microwave irradiation provides a relatively rapid means of effecting *N*-alkylations of isatin with a variety of benzylic halides, propargyl bromide and ethyl bromoacetate in times ranging from 10-25 min at 140 ^{o}C in closed vials. This report involves the first reported use of DBU for this purpose, and in contrast to other methods, allows for the facilitated isolation of pure products while avoiding extractive or chromatographic purification steps.

Keywords: Isatin, *N*-alkylation, microwave, DBU, expedited synthesis

Introduction

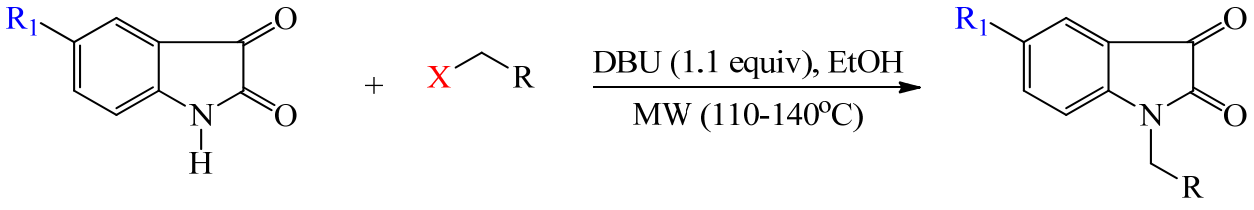
Increased attention is being devoted to exploiting the chemistry[1,2] and bioactivity[3] of the highly diversifiable isatin nucleus.[4,5] The "privileged"[6] nature of this scaffold and its central role as progenitor to other classes of biologically active heterocycles,[7,8] provides incentive for the development of expedient protocols for the embellishment of this core structure, especially in terms of *N*-alkylation.[9] To that end, several groups have devised parallel methods for such an operation, minimizing purification and amenable to automation under thermal or microwave conditions. Noteworthy examples include a parallel microwave procedure employing K_2CO_3/KI in acetonitrile (160 ^{o}C, 10 min)[10] and an analogous process in DMF (150 ^{o}C, 5-15 min).[11]

Alternatively, with regard to devising highly efficient and rapid solution phase methodologies for the parallel synthesis of diverse isatins, Shuttleworth utilized polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) on polystyrene for the preparation of a library of serine protease inhibitors,[12] while

Chibale *et al.* employed the less expensive solid-supported base potassium fluoride on alumina (KF/Al_2O_3).[13] More recently, we reported the use of KF/Al_2O_3 in acetonitrile (ACN) for the *N*-alkylation of isatins under thermal conditions or microwave-irradiation (180 °C).[14] Whereas all three of the above methods allow for facilitated purification by filtration from the solid bases employed, they also necessitated standard means of workup or purification after that point. It was therefore envisaged that if a soluble organic base were employed in a solvent from which the product might spontaneously crystallize, a substantial saving in time-consuming steps would be realized.

Results and Discussion

In devising highly efficient and rapid solution phase methodologies for the parallel preparation of diverse isatins, it was envisaged that the use of a soluble base under microwave conditions might constitute a useful expedient. Since it appeared that the *N*-alkylation of isatin had yet to be conducted under microwave irradiation using DBU, it was decided to examine the use of this basic catalyst in ethanol (EtOH) under microwave irradiation in a CEM Discover microwave (300 watts). The initial parameters involved using DBU (1.1 equiv) for the model reaction of isatin (0.3 g, 2.00 mmol) and benzyl chloride (1.5 equiv) to yield 1-benzylindoline-2,3-dione in EtOH (3 mL) in a microwave vial (10 mL). Reactions were conducted at temperatures from 120°C to 140°C in 10 degree increments and at time intervals of 10 and 25 min after which reactions were monitored by GC/MS to ascertain completeness. For the prototype reaction above, it was found that complete conversion was effected at 140°C for 10 min. Using these optimal parameters for temperature and time, it was found that increasing the amount of DBU to 1.5 equiv did not result in substantially enhanced conversion. Therefore, these conditions were employed to conduct other *N*-alkylation reactions using isatin and DBU to produce the desired *N*-alkylated isatins (Scheme 1).

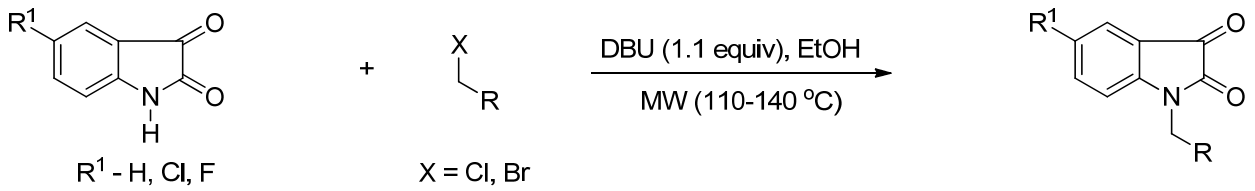


R_1 = H, Cl, F X = Cl, Br

Table 1 displays a summary of the microwave irradiation process providing a rapid means of effecting *N*-alkylations of isatins with a variety of benzylic halides, propargyl bromide, and ethyl bromoacetate. The yields listed are a summation of the pure solid obtained upon the first crystallization and that obtained by chromatographic purification of the filtrate. In all instances, the material obtained by crystallization from the reaction medium was pure, as determined by

GC/MS and in most cases provided sufficient amounts of material to be carried on in subsequent steps if desired.

In general, alkylation of isatins bearing electron-withdrawing substituents at the C-5 position could be effected at lower temperatures albeit with longer reaction times. Additionally, electron withdrawing groups on the benzylic halides also served to enhance observed reactivity in comparison to those rings not similarly substituted or the propargyl halide. In the case of the *N*-propargylation of isatin itself (entry 2), it was determined that the use of a ramp technique in the microwave allowed for a higher yield but such a protocol was unnecessary in other reactions. It is also noteworthy that ethyl 2-(5-chloro-2,3-dioxoindolin-1-yl)acetate (6) formed rapidly at room temperature upon mixing of the reactants.



Scheme 1

Table 1. Optimization of reaction conditions

Entry	Substituents in Scheme 1		Time (min)	Temp. (°C)	MP (°C)	Yield	Lit. MP (°C)
	R^1	R					
1	H	CO_2Et	10	140	105-110	47%	124-129[14]
2	H	C≡CH	10	140	147-149	81%	157-158[15]
3	H	Ph	10	140	129-134	61%	128-133[14]
4	H	2,6-$Cl_2C_6H_3$	10	140	181-186	93%	175-180[14]
5	H	2,6-$F_2C_6H_3$	10	140	155-158	84%	154-156[14]
6	Cl	CO_2Et	20	120	126-128	68%	130-135[14]
7	Cl	C≡CH	20	120	157-159	64%	Ref. 16
8	Cl	Ph	20	120	130-133	71%	134[14]
9	Cl	2,6-$Cl_2C_6H_3$	20	120	232-235	84%	233-235[14]
10	Cl	2,6-$F_2C_6H_3$	20	120	171-174	72%	172-177[14]
11	F	Ph	25	120	128-131	88%	130-133[17]
12	F	2,6-$F_2C_6H_3$	25	120	132-134	82%	Ref. 10

Thus, the use of the soluble base DBU in conjunction with a suitable crystallizing solvent under microwave conditions allows for the expedited construction of a small library of *N*-alkylated isatins which could be isolated in a pure state and in synthetically useful yields by simple filtration.

Conclusions

The development of a convenient synthesis of *N*-alkylated isatins with various alkyl halides under microwave irridiation was examined using the soluble liquid base DBU. With the use of this soluble base, an expedited synthetic protocol was devised wherein product isolation could be effected by simple filtration of the reaction mixture.

Experimental Section

General. Melting points were determined via the use of open capillaries with an Electrothermal melting point apparatus. The ^{1}H and ^{13}C NMR data were obtained on a Bruker Avance 300 MHz NMR in DMSO-d_6 solution. Chemical shifts for proton NMR are reported in δ (ppm) downfield from tetramethylsilane as an internal standard and ^{13}C NMR shifts are calibrated on the DMSO-d_6 resonance at 39.50 ppm. Coupling constants (*J*) are in Hz. The following abbreviations are used to describe peak patterns where appropriate: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; dt, double triplet; m, multiplet. GC/MS measurements were performed using Hewlett-Packard 6890 Series GC with auto injection and mass fragments are reported as mass per charge, *m/z*. The GC was coupled with a mass spectrometer with Hewlett-Packard 5973 mass selective detector/quadrupole system. Flash column (Silica Gel, Premium R_f, 200-400 mesh, Sorbent Technologies) and thin layer chromatography reactions were performed on silica gel with indicated solvent systems. Microwave reactions were performed in a monomode MARS Glasschem 300 Watt system by CEM with sample absorption set to "normal".
Note: Identities of compounds previously prepared in this laboratory[14] were confirmed by GC/MS as well as ^{1}H and ^{13}C NMR comparisons.

Ethyl 2-(2,3-dioxoindolin-1-yl)acetate (1). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added isatin (0.3111 g, 2.11 mmol), DBU (325 µL, 1.1 eq) and ethyl bromoacetate (257 µL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 10 min at 140 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was allowed to stand overnight in a freezer and then vacuum filtered to afford the pure (TLC, GC/MS) product as a light orange solid (0.1049 g, 21%): mp 105-110 ºC (lit.[14]mp 124-129 °C); R_f = 0.21 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford an oil which was purified by silica gel

chromatography (hexanes/EtOAc, 70:30) to provide additional product (0.1130 g) for a combined overall yield of 47%; ^{1}H NMR (300 MHz DMSO-d_6) δ 7.62 (td, J = 7.83 Hz, 1.35 Hz, 1H), 7.55 ppm (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.20 (td, J = 7.5 Hz, 0.7 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 4.54 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz DMSO-d_6) δ 182.3, 167.1, 158.2, 150.1, 138.5, 124.5, 123.7, 117.3, 111.3, 61.3, 41.1, 14.0 ppm; MS (*m/z*) 233 (M^+), 132 (100%).

1-(Prop-2-yn-1-yl)indoline-2,3-dione (2). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added isatin (0.3064 g, 2.08 mmol), DBU (342 µL, 1.1 eq) and propargyl bromide (210 µL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in dynamic mode where the mixture was heated in 5 stages with pressure and high power being held constant throughout the run time at 130 psi and 200 watts, respectively. The first stage of heating was set at 110 °C for 3 min, the second stage of heating was set at 120 °C for 2 min, the third stage of heating was set at 100 °C for 1 min, the fourth stage of heating was set at 120 °C for 2 min, and the final stage of heating was set at 95 °C for 6 min. The first stage had high stirring while the final 4 stages had a low stir setting. The pre-stirring for this setup was high for 1 min. After cooling to rt, the reaction vessel was placed in the freezer overnight and vacuum-filtered to afford the pure product (GCMS/TLC) as an orange solid (0.1277 g, 33.1%): mp 147–149 °C (lit.[15]mp 157-158 °C); R_f = 0.46 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure and purified by silica gel chromatography (hexanes/EtOAc, 70:30) to give additional product (0.1844 g) for a combined overall yield of 81%; ^{1}H NMR (300 MHz DMSO-d_6) δ 7.75 (td, J = 1.3 Hz, J = 7.8 Hz, 1H), 7.61 (dd, J = 0.5 Hz, J = 1.2 Hz, 1H), 7.58 (dd, J = 0.5 Hz, J = 1.2 Hz, 1H), 7.24 (d, J =7.9 Hz, 1H), 7.21 (dd, J = 0.8 Hz, J = 15.0 Hz, 1H), 7.19 (d, J = 0.7 Hz, 1H), 4.55 (d, J = 2.5 Hz, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 182.5, 157.3, 149.4, 138.1, 124.5, 123.6, 117.6, 111.1, 77.2, 74.8, 28.9; MS: *m/z* 185 (M^+), 129 (100%).

1-Benzylindoline-2,3-dione (3). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added isatin (0.2943 g, 2.00 mmol), DBU (329 µL, 1.1 eq) and benzyl chloride (257µL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 10 min at 140 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was allowed to stand overnight in a freezer and then vacuum filtered to afford the pure (TLC, GC/MS) product as a light orange solid (0.0536 g, 11%): mp 129-134 °C (lit.[14]mp 128-133 °C); R_f = 0.41 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford an oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to provide additional product (0. 2895 g) for a combined overall yield of 61%; 1H NMR (300 MHz DMSO-d_6) δ 7.60 (td, J = 7.8 Hz, 1.3 Hz, 1H), 7.44 (dd, J = 7.2 Hz, 0.8 Hz, 1H), 7.37-7.28 (m, 5-H), 7.14 (td, J = 7.5 Hz, 0.8 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 4.91 (s, 1H); ^{13}C NMR (75 MHz DMSO-d_6) δ 183.1, 158.3, 150.3, 137.9, 135.5, 128.6, 127.5, 127.3, 124.4, 123.3, 117.7, 111.0, 42.9; MS (*m/z*) 237 (M^+), 146 (100%).

1-(2,6-Dichlorobenzyl)indoline-2,3-dione (4). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added isatin (0.3062 g, 2.08 mmol), DBU (342 µL, 1.1 eq) and 2,6-dichlorobenzyl bromide (0.5711 g, 1.1 eq). The reaction vessel was sealed and heated

under microwave irradiation in standard mode for 10 min at 140 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was allowed to stand overnight in a freezer and then vacuum filtered to afford the pure (TLC, GC/MS) product as an orange solid (0.4151 g, 65%): mp 181-186 ºC (lit.[14]mp 175-180 °C); R_f = 0.57 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure and purified by silica gel chromatography (hexanes/EtOAc, 70:30) to provide additional product (0.1787 g) for a combined overall yield of 93%; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.58 ppm (dd, *J* = 7.5 Hz, 0.8 Hz, 1H), 7.44 (d, *J* = 8.31Hz, 1H), 7.15 (d, *J* = 7.23Hz, 1H), 7.13 (t, *J* = 6.51Hz, 1H), 7.08 (t, *J* = 7.56Hz, 1H), 6.93 (d, *J* = 7.89Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 182.7, 157.7, 150.6, 138.4, 135.4, 130.8, 129.7, 129.1, 124.7, 123.4, 117.9, 110.8, 40.4; MS (*m/z*) 305 (M^+), 270 (100%).

1-(2,6-Difluorobenzyl)indoline-2,3-dione (5). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added isatin (0.2962 g, 2.01 mmol), DBU (329 µL, 1.1 eq) and 2,6-difluorobenzyl bromide (0.5278 g, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 10 min at 140 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was allowed to stand overnight in a freezer and then vacuum filtered to afford the pure (TLC, GC/MS) product as yellow-orange solid (0.2469 g, 45%): mp 155-158 ºC (lit.[14]mp 154-156 °C); R_f = 0.32 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford an oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to provide additional product (0.2100 g) for a combined overall yield of 84%; ^{1}H NMR (300 MHz DMSO-d_6) δ 7.70 (t, *J* = 7.8 Hz, 1H),7.57 ppm (dd, *J* = 7.5 Hz, 0.8 Hz, 1H), 7.49 (m, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 8.2 Hz, 1H), 4.96 (s, 1H); ^{13}C NMR (75 MHz DMSO-d_6) δ: 182.8, 162.7-159.3 (dd, *J* = 7.8 Hz), 157.6, 150.3, 138.3, 130.8-130.6 (t, *J* = 10.4 Hz), 124.6, 123.4, 117.6, 111.9-111.65 (d, *J* = 7.4 Hz), 110.8, 110.40-110.36 (t, *J* = 7.8 Hz), 32.1; MS (*m/z*): 273 (M^+), 146 (100%).

Ethyl 2-(5-chloro-2,3-dioxoindolin-1-yl)acetate (6). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added 5-chloroisatin (0.3689 g, 2.00 mmol), DBU (329 µL, 1.1 eq) and ethyl bromoacetate (243 µL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 20 min at 120 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was allowed to stand overnight in a freezer and then vacuum filtered to afford the pure (TLC, GC/MS) product as a light orange solid (0.1662 g, 31%): mp 126-128 ºC (lit.[14]mp 130-135 °C); R_f = 0.63 (hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford an oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to provide additional product (0.1965 g) for a combined overall yield of 68%; ^{1}H NMR (300 MHz DMSO-d_6) δ 7.77 ppm (dd, *J* = 8.6 Hz, 2.2 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 4.62 (s, 2H), 4.20 (q, 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz DMSO-d_6) δ 181.5, 167.3, 157.8, 148.9, 137.3, 127.9, 124.1, 118.6, 112.9, 61.4, 41.3, 13.9; MS (*m/z*) 267 (M^+), 28 (100%).

5-Chloro-1-(prop-2-yn-1-yl)indoline-2,3-dione[16] (7). To a 10 mL microwave vial charged with ethanol (3mL) and a magnetic stir bar was added isatin (0.3632 g, 2.00 mmol), DBU (329 µL,

1.1 eq) and propargyl bromide (201 μL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 20 min at 110 °C with pre-stirring 30 sec. After cooling to rt, the reaction vessel was placed in the freezer overnight and then vacuum filtered to afford a pure (GCMS/TLC) orange solid (0.0521 g, 12%): mp 157-159 ºC; R_f = 0.51(hexanes/EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford an orange oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to give additional product (0.3145 g) for a combined overall yield of 64%: ^{1}H NMR (300 MHz DMSO-d_6) δ 7.79 (dd, J = 2.2 Hz, J = 8.4 Hz, 1H), 7.65 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 4.56 (d, J = 2.5 Hz, 2H), 4.35 (t, J = 5.0, 1H); ^{13}C NMR (75 MHz DMSO-d_6) δ 181.4, 157.1, 147.9, 136.9, 127.8, 124.0, 119.1, 112.8, 77.0, 75.1, 29.1; MS (*m/z*) 219 (M^+), 28 (100 %). Anal. Calcd for $C_{11}H_6ClNO_2$: C, 60.16; H, 2.75; N, 6.38; Found: C, 59.98; H, 2.73; N, 6.33.

1-Benzyl-5-chloroindoline-2,3-dione (8). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added 5-chloroisatin (0.3785 g, 2.08 mmol), DBU (329 μL, 1.1 eq) and benzyl chloride (257 μL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 20 min at 140 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was placed in the freezer overnight but did not afford a solid. The resulting orange-red liquid was then evaporated under reduced pressure to afford an orange oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to afford a pure (GC-MS/TLC) orange red solid (0.3875 g, 71%): mp 130-133 ºC (lit.[14]mp 134 °C); R_f = 0.65 (hexanes:EtOAc,1:1). ^{1}H NMR (300 MHz DMSO-d_6) δ 7.63 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 7.44 ppm (d, J = 2.2 Hz, 1H), 7.37-7.28 (m, 5-H), 6.98 (d, J = 8.3 Hz, 1H), 4.91 (s, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 181.9, 158.1, 148.8, 136.7, 135.1, 129.7, 128.6, 127.5, 127.2, 123.9, 119.1, 112.6, 42.9; MS (*m/z*) 271 (M^+), 180 (100%).

1-(2,6-Dichlorobenzyl)-5-chloroindoline-2,3-dione (9). To a 10 mL microwave vial charged with ethanol (3 mL) a magnetic stir bar was added 5-chloroisatin (0.3658 g, 2.01 mmol), DBU (329 μL, 1.1 eq) and 2,6-dichlorobenzyl bromide (0.5310 g, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 20 min at 120 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was placed in the freezer for 2 h and then vacuum filtered to afford the pure (TLC, GC/MS) product as an orange-red solid (0.5772 g, 84%): mp 232-235 ºC (lit.[14]mp 233-235 °C); R_f = 0.60 (hexanes/EtOAc, 1:1). ^{1}H NMR (300 MHz DMSO-d_6) δ 7.73 ppm (dd, J = 8.5 Hz, 2.3 Hz, 1H), 7.65 (d, J = 2.3 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.44 (t, 7.9 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 181.6, 157.5, 149.2, 137.3, 135.4, 130.8, 129.5, 129.1, 127.6, 124.2, 118.9, 112.6, 40.4; MS (*m/z*) 339 (M^+), 180 (100%).

1-(2,6-Difluorobenzyl)-5-chloroindoline-2,3-dione (10). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added 5-chloroisatin (0.3650 g, 2.00 mmol), DBU (329 μL, 1.1 eq) and 2,6-difluorobenzyl bromide (0.4554 g, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 20 min at 120 °C with a pre-stirring 30 sec. After cooling to rt, the reaction vessel was placed in the freezer overnight and then vacuum filtered to afford the pure (TLC, GC/MS) product as a red solid (0.4091 g, 66%):

mp 171-174 ºC (lit.[14]mp 172-177 °C); R_f = 0.56 (hexanes:EtOAc, 1:1). A second crop afforded additional product (0.0339 g) for a combined overall yield of 72%. ^{1}H NMR (300 MHz DMSO-d_6) δ 7.76 ppm (dd, *J* = 2.2 Hz, *J* = 8.5 Hz, 1H), 7.63 (d, 2.2 Hz, 1H), 7.49-7.39 (m, 1H), 7.15 (t, *J* = 8.2 Hz, 1H), 7.10 (d, 8.6 Hz, 1H), 4.94 (s, 2H) ^{13}C NMR (75 MHz DMSO-d_6) δ 181.7, 162.7-159.4 (dd, *J* = 8.2 Hz), 157.5, 148.8, 137.1, 130.9-130.6 (t, *J* = 10.5 Hz), 127.6, 124.0, 119.0, 112.2-112.1 (t, *J* = 2.6 Hz), 111.9-111.6 (d, *J* = 17.8 Hz), 110.6, 32.2; MS (*m/z*) 307 (M^+), 127 (100%).

1-Benzyl-5-fluoroindoline-2,3-dione (11). To a 10 mL microwave vial charged with ethanol (3 mL) and a magnetic stir bar was added 5-fluoroisatin (0.3310 g, 2.00 mmol), DBU (330 μL, 1.1 eq) and benzyl chloride (254 μL, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 25 min at 120 °C with a pre-stirring of 30 sec. After cooling to room temperature, the reaction vessel was placed in the freezer overnight and then vacuum filtered to afford a pure (GCMS/TLC) dark red solid (0.1408 g, 28%): mp 128-131 ºC (lit.[17]mp 130-133 °C); R_f = 0.64 (hexanes:EtOAc, 1:1). The filtrate was then evaporated under reduced pressure to afford a red oil which was purified by silica gel chromatography (hexanes/EtOAc, 70:30) to give a dark red solid (0.3073 g) for a combined overall yield of 88%: ^{1}H NMR (300 MHz DMSO-d_6) δ 7.57 ppm (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.2 Hz, 2.2 Hz, 1H), 7.39-7.28 (m, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 4.94 (s, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 182.4, 160.09-156.86 (d, *J* = 241 Hz), 158.35-158.33 (d, *J* = 1.4 Hz), 146.5-146.4 (d, *J* = 1.6 Hz), 135.3, 128.6, 127.5, 127.3, 123.9-123.6 (d, *J* = 24.0 Hz), 118.7-118.6 (d, *J* = 7.2 Hz), 112.4-112.3 (d, *J* = 7.4 Hz), 111.6-111.3 (d, *J* = 24.3 Hz), 42.9; MS (*m/z*) 255 (M^+), 164 (100%).

1-(2,6-Difluorobenzyl)-5-fluoroindoline-2,3-dione[10] (12). To a 10 mL microwave vial charged with ethanol (3mL) and a magnetic stir bar was added 5-fluoroisatin (0.3294 g, 1.99 mmol), DBU (329 μL, 1.1 eq) and 2,6-difluorobenzyl bromide (0.4594 g, 1.1 eq). The reaction vessel was sealed and heated under microwave irradiation in standard mode for 25 min at 120 °C with a pre-stirring of 30 sec. After cooling to rt, the reaction vessel was placed in the freezer overnight and then vacuum filtered to afford a dark red solid (0.2133 g, 37%): mp 132-134 °C. The filtrate was then evaporated under reduced pressure to afford a red oil which was purified by silica gel chromatography (hexanes/EtOAc,70:30) to give additional product (0.2612 g) for a combined overall yield of 82%; ^{1}H NMR (300 MHz, DMSO): δ .7.60 (ddd, *J* = 2.8 Hz, *J* = 8.7 Hz, 1H), 7.49 (dd, *J* = 2.7 Hz, *J* = 7.0 Hz, 1H), 7.44 (dd, *J* = 1.7 Hz, *J* = 6.8 Hz, 1H) 7.15 (t, 3H), 7.25 (dd, *J* = 2.7 Hz, *J* = 8.6 Hz, 1H), 6.98 (t, *J* = 8.1 Hz, 1H), 6.91 (dd, *J* = 3.5 Hz, *J* = 8.6 Hz, 1H), 4.96 (s, 2H); ^{13}C NMR (75 MHz DMSO-d_6) δ 182.19-182.16 (d, *J* = 2.1 Hz), 167.7, 162.6-159.2 (dd, *J* = 7.7 Hz), 160.0-156.8 (d, *J* = 241 Hz), 157.73-157.71 (d, *J* = 1.7 Hz), 146.56-146.54 (d, *J* = 1.6 Hz), 130.9-130.6 (t, *J* = 10.5 Hz), 124.41-124.0 (d, *J* = 24.1 Hz), 118.5-118.4 (d, *J* = 7.1 Hz), 111.9-111.7 (d, *J* = 7.3 Hz), 111.6-111.4 (d, *J* = 17.7 Hz), 110.9-110.4 (t, *J* = 18.7 Hz), 32.2 (t, *J* = 3.9 Hz); MS (*m/z*) 291 (M^+), 164 (100%).

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