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ASSEMBLY OF SUBSTITUTED HOMOPHTHALIMIDES *VIA* CuI-CATALYZED COUPLING OF 2-BROMOBENZAMIDES WITH β-KETO ESTER

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Abstract – CuI catalyzed coupling of 2-bromobenzamides and β-keto esters takes place at 90 °C in *i*-PrOH to afford substituted homophthalimides in good yields. This transformation undergoes a cascade coupling/intramolecular condensation process, which allows assembly of a wide range of substituted homophthalimides by varying 2-bromobenzamides and β-keto esters.

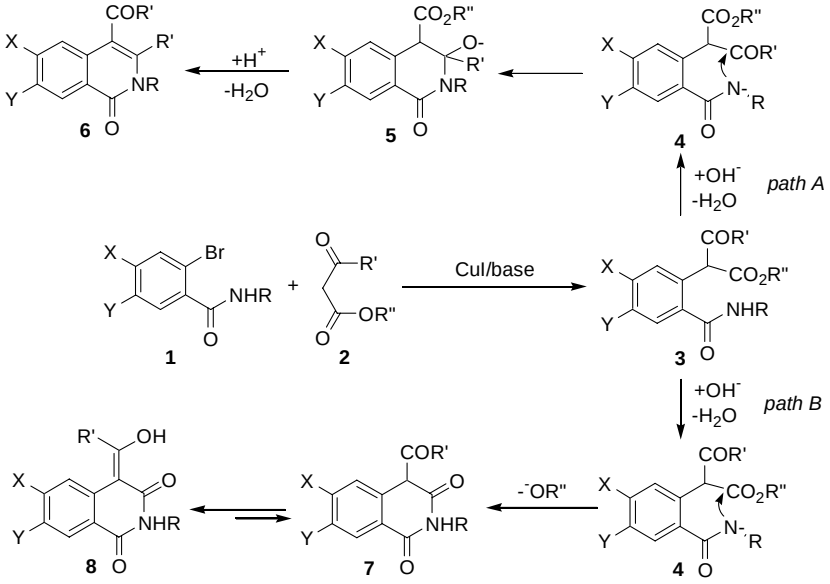
INTRODUCTION

Many biologically and pharmaceutically important molecules contain a homophthalimide moiety, which possess a wide range of biological activities from blocking auxin transport[1] to inhibiting human rhinovirus 3C protease,[2] cyclooxygenase,[3] nitric oxide synthease,[4] and cyclin-dependent kinase 4.[5] Normally, these compounds were prepared *via* condensation of homophthalic anhydride with amines and subsequent introduction of functional groups.[1-6]

RESULTS AND DISCUSSION

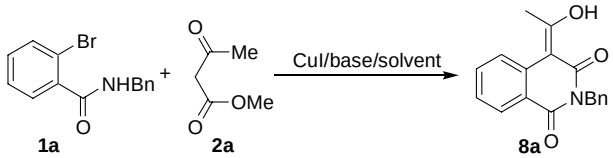
In recent years we have witnessed great progress on development of mild conditions for copper-catalyzed cross-coupling reaction of aryl halides and activated methylene compounds.[7] This advantage allowed us to establish some new methods for elaboration of heterocycles like polysubstituted indoles, benzofurans, 3-acyloxindoles and isoquinolines.[8] As an extension of this work, in this paper, we explored the possibility of CuI-catalyzed coupling reaction of 2-bromobenzamides with β-keto esters. We envisaged that if the coupling reaction proceeds smoothly (Scheme 1), its products **3** may undergo an intramolecular condensation to afford substituted 1(2*H*)-isoquinolones **6** (*via* attacking the ketone group and subsequent

dehydration, path A), or substituted homophthalimides **7** and their isomer **8** (*via* attacking the ester group, path B).



Scheme 1. Coupling of 2-bromobenzamides with β-keto esters and subsequent possible condensations

Table 1. CuI-catalyzed coupling of *N*-benzyl 2-bromobenzamide **1a** with methyl acetoacetate **2a** under different conditions[a]



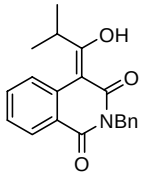
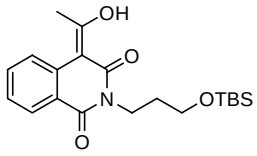
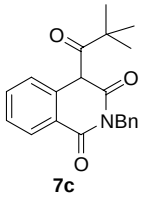
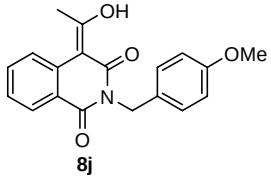
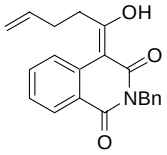
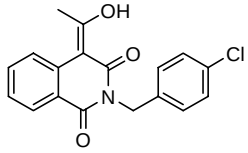
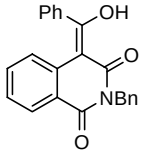
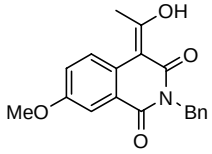
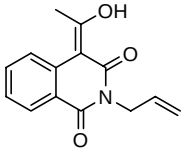
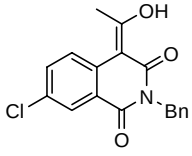
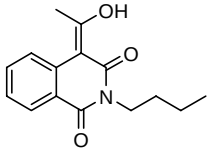
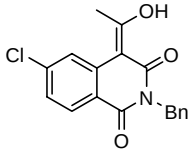
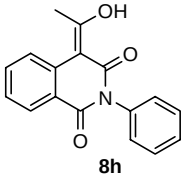
entry	base	solvent	T (^{o}C)	t (h)	yield (%)[b]
1	K_2CO_3	*i*-PrOH	70	22	53(12[c])
2	K_2CO_3	toluene	70	22	33(56[c])
3	K_2CO_3	dioxane	70	22	39(48[c])
4	K_2CO_3	THF	70	22	38(25[c])
5	K_3PO_4	*i*-PrOH	70	22	55
6	Cs_2CO_3	*i*-PrOH	70	22	63
7	Cs_2CO_3	*i*-PrOH	90	22	65
8	Cs_2CO_3	*i*-PrOH	90	21	85[d]
9	Cs_2CO_3	*i*-PrOH	90	23	70[e]

[a]Reaction conditions: *N*-benzyl 2-bromobenzamide **1a** (0.5 mmol), methyl acetoacetate (1 mmol), CuI (0.05 mmol), base (1.5 mmol), solvent (1.5 mL). [b]Isolated yield. [c]**1a** was recovered. [d]2 mmol of Cs_2CO_3 was used. [e]0.75 mmol of methyl acetoacetate was used.

With this idea in mind, a coupling reaction of *N*-benzyl 2-bromobenzamide **1a** with methyl acetoacetate **2a** was conducted under our previous conditions (10 mol % CuI, 300 mol % K_2CO_3 in *i*-PrOH). We were pleased to find that after 22 h at 70 ^{o}C, homophthalimide **8a** was isolated in 53% yield (entry 1, Table 1). Changing solvent to toluene, dioxane or THF gave worse results (entries 2-4). The yield was improved by

switching base to K_3PO_4 (entry 5), and further improved by using Cs_2CO_3 (entry 6). After failed in increasing the yield by raising the reaction temperature (entry 7), we found that ideal yield could be obtained by increasing the amount of the base to 4 equiv (entry 8). The amount of methyl acetoacetate was also important as evident from that only 70% yield of **8a** was obtained when 1.5 equiv of this ester was used (entry 9). The structure of **8a** was established by X-ray analysis (Figure 1).

Table 2. Elaboration of substituted homophthalimides[a]

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	 **8b**	81	8	 **8i**	71
2	 **7c**	82	9	 **8j**	80
3	 **8d**	74	10	 **8k**	85
4	 **8e**	84	11	 **8l**	52
5	 **8f**	60	12	 **8m**	79
6	 **8g**	60	13	 **8n**	92
7	 **8h**	87			

[a]Reaction conditions: bromobenzamide (0.5 mmol), β-keto ester (1 mmol), CuI (0.05 mmol), Cs_2CO_3 (2 mmol), *i*-PrOH (1.5 mL). [b]Isolated yield.

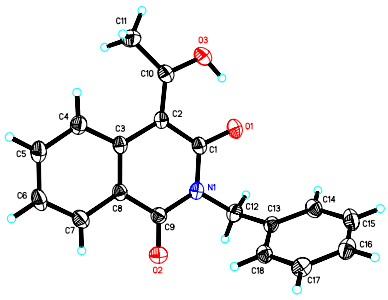
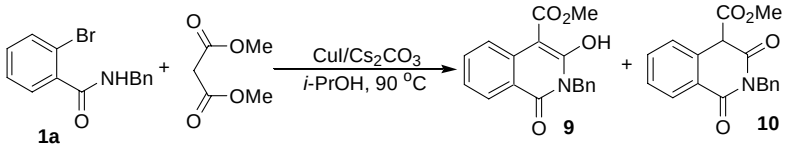


Figure 1. X-Ray structure of **8a**

The optimized reaction conditions were further applied to other 2-bromobenzamides with β-keto esters and the results are summarized in Table 2. Generally, they all gave good yield of the corresponding homophthalimide as an enol form, which demonstrated that after coupling the intramolecular condensation took place exclusively between the ester and amide moieties (path B). In case of *t*-butyl substituted β-keto ester as a starting material, a homophthalimide was obtained in keto form (entry 2), while *i*-propyl substituted β-keto ester gave the corresponding homophthalimide as a mixture of enol and ketone forms in a ratio of about 10:1 (entry 1). These results indicated that the steric hindrance has great influence to the balance between ketone form and enol form products. The steric hindrance of the ketone part seems to have little effect to reaction yields because almost identical yields were observed for products **8a**, **8b** and **7c** (entries 1 and 2). The olefin embodied and phenyl substituted β-keto esters also worked under these conditions, delivering homophthalimides **8d** and **8e** in good yields (entries 3 and 4). Additionally, variation of the N-substituents of homophthalimides **8f-k** could be achieved by changing the N-substitutents of 2-bromobenzamides (entries 5-10). Furthermore, homophthalimides **8l-n** were obtained in 52-92% yields (entries 11-13), indicating that functionalization at the aromatic ring of homophthalimides is possible using our method. Taken together, we concluded that the present method could elaborate substituted homophthalimides with considerable diversity.

When dimethyl malonate was used as a coupling partner, ester substituted homophthalimide **9** was obtained. In this case enol form product was observed as a major isomer while ketone form product **10** was determined as a minor isomer. The ratio for these two isomers was about 7.5:1.



Scheme 2. Coupling of *N*-benzyl 2-bromobenzamide with dimethyl malonates

In conclusion, we have developed a cascade coupling/intramolecular condensation process to assemble substituted homophthalimides from 2-bromobenzamides and β-keto esters. This method provides a convenient route for synthesizing these biologically important heterocycles with considerable diversity. Thus, it may find application in organic synthesis.

EXPERIMENTAL

General procedure for synthesis of substituted substituted homophthalimides (8). An oven-dried Schlenk tube was charged with CuI (19 mg, 0.1 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol), and *N*-benzyl-*o*-bromobenzamide **1** (1 mmol). The tube was evacuated and backfilled with argon (3 times), and then β-keto ester **2** (2.0 mmol) and *i*-PrOH (3.0 mL) was added. The reaction mixture was stirred at 90 ^{o}C for 21-24 h. The cooled solution was poured into 1N HCl, extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with 5:1 to 1:1 petroleum ether/EtOAc) and the product was dried under vacuum for at least 1 h.

2-Benzyl-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8a) White solid, mp 124-125 ^{o}C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.8 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.58-7.60 (m, 2H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.23-7.37 (m, 4H), 5.30 (s, 2H), 2.61(s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 179.4, 166.5, 159.4, 133.1, 130.1, 129.4, 125.8, 125.1, 124.7 (2×C), 123.8 (2×C), 121.7, 120.4, 119.1, 96.3, 39.8, 21.6. **EI-MS** *m/z* 293 (M^+); **EI-HRMS** calcd for $C_{18}H_{15}NO_3$ (M^+) 293.1052, found 293.1053.

2-Benzyl-4-(1-hydroxy-2-methylpropylidene)-4*H*-isoquinoline-1,3-dione (8b) White solid; mp 133-134 ^{o}C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ Enol form: 16.7 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.47-7.58 (m, 4H), 7.23-7.36 (m, 4H), 5.31 (s, 2H), 3.51-3.59 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 6H); Keto form: 8.27 (d, *J* = 8.1 Hz, 1H), 7.47-7.58 (m, 4H), 7.23-7.36 (m, 4H), 5.28 (s, 1H), 5.18-5.23 (m, 2H), 2.93-3.00 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 190.0, 170.3, 163.2, 136.8, 133.6, 133.0, 129.3, 128.7 (2×C), 128.6, 128.3, 127.4, 125.3, 124.1, 123.0, 98.6, 43.4, 32.9, 19.9 (2×C). **EI-MS** *m/z* 321 (M^+); **EI-HRMS** calcd for $C_{20}H_{19}NO_3$ (M^+) 321.1365, found 321.1367.

2-Benzyl-4-(pivaloyl)-4*H*-isquinoline-1,3-dione (7c) White solid; mp 116-117 ^{o}C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.44-7.52 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.20-7.29 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 1H), 5.62 (s, 1H), 5.14 (d, *J* = 13.8 Hz, 1H), 5.07 (d, *J* = 13.8 Hz, 1H), 1.27 (s, 9H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 204.8, 167.6, 165.0, 136.6, 133.9, 133.3 (2×C), 129.5, 128.4, 128.3 (2×C), 128.2, 127.3, 126.9, 126.0, 56.2, 46.4, 43.8, 26.3 (3×C). **EI-MS** *m/z* 335 (M^+); **EI-HRMS** calcd for $C_{21}H_{21}NO_3$ (M^+) 335.1521, found 335.1529.

2-Benzyl-4-(1-hydroxypent-4-enylidene)-4*H*-isoquinoline-1,3-dione (8d) White solid; mp 99-100 ^{o}C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.9 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.21-7.63 (m, 8H), 5.84-5.98 (m,

1H), 5.31 (s, 2H), 5.06-5.19 (m, 2H), 3.02 (t, *J* = 7.5 Hz, 2H), 2.55-2.63 (m, 2H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 185.4, 170.2, 163.1, 136.8, 136.4, 133.5, 133.1, 129.5, 128.7 (2×C), 128.5, 128.4, 127.5, 125.4, 124.0, 122.8, 116.0, 99.9, 43.5, 36.0, 29.8. **ESI-MS** *m/z* 334.2 $(M + Na)^+$; **ESI-HRMS** calcd for $C_{21}H_{19}NO_3$ $(M + Na)^+$ 356.12572, found 356.1256.

2-Benzyl-4-(hydroxyphenylmethylene)-4*H*-isoquinoline-1,3-dione (8e)[9] Yellow solid; mp 105-106 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.7 (s, 1H), 8.24 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42-7.56 (m, 7H), 7.10-7.35 (m, 5H), 6.81 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 2H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 180.5, 170.5, 163.3, 136.7, 136.1, 133.4, 131.9, 131.5, 129.0, 128.9, 128.8 (2×C), 128.7, 128.6 (2×C), 128.4 (2×C), 127.6, 125.6, 125.5, 122.9, 99.1, 43.6. **ESI-MS** 356.2 $(M + H)^+$; **ESI-HRMS** calcd for $C_{23}H_{17}NO_3Na$ $(M + Na)^+$ 378.11007, found 378.1100.

2-Allyl-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8f) White solid; mp 87-88 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.8 (s, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.60-7.63 (m, 2H), 7.33-7.38 (m, 1H), 5.88-6.01 (m, 1H), 5.26 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.20 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.73 (d, *J* = 5.7 Hz, 2H), 2.64 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.0, 169.9, 162.8, 133.8, 133.1, 131.8, 129.4, 125.3, 124.0, 122.7, 117.6, 99.9, 42.3, 25.2. **ESI-MS** *m/z* 244.0 $(M + H)^+$; **ESI-HRMS** calcd for $C_{14}H_{14}NO_3$ $(M + H)^+$ 244.09682, found 244.0974.

2-Butyl-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8g)[10] White solid; mp 62-63 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 17.0 (s, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.59-7.60 (m, 2H), 7.32-7.37 (m, 1H), 4.10 (t, *J* = 7.5 Hz, 2H), 2.63 (s, 3H), 1.61-1.74 (m, 2H), 1.37-1.45 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.0, 170.2, 163.0, 133.7, 132.9, 129.2, 125.2, 123.9, 122.8, 99.8, 40.2, 29.9, 25.3, 20.3, 13.7. **ESI-MS** *m/z* 260.2 $(M+H)^+$; **ESI-HRMS** calcd for $C_{15}H_{18}NO_3$ $(M + H)^+$ 260.12812, found 260.1285.

4-(1-Hydroxyethylidene)-2-phenyl-4*H*-isoquinoline-1,3-dione (8h) White solid; mp 168-169 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.5 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 4.2 Hz, 2H), 7.37-7.57 (m, 4H), 7.25-7.27 (m, 2H), 2.69 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.6, 170.7, 163.5, 135.1, 134.3, 133.7, 129.9, 129.7 (2×C), 129.1, 128.7 (2×C), 125.8, 124.6, 123.4, 100.4, 25.5. **EI-MS** *m/z* 279 (M^+); **EI-HRMS** calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158, found 323.1146.

2-[3-(tert-Butyldimethylsilanyloxy)propyl]-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8i) Colorless oil;. **^{1}H NMR** (300 MHZ, $CDCl_3$): δ 17.0 (s, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.59-7.60 (m, 2H), 7.31-7.37 (m, 1H), 4.19 (t, *J* = 7.5 Hz, 2H), 3.73 (t, *J* = 6.3 Hz, 2H), 2.62 (s, 3H), 1.86-1.95 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.0, 170.2, 163.0, 133.7, 132.9, 129.3, 125.2, 124.0, 122.8, 99.9, 61.2, 38.1, 31.0, 25.8 (3×C), 25.3, 18.2, -5.4 (2×C). **EI-MS** *m/z* 375 (M^+); **EI-HRMS** calcd for $C_{20}H_{29}NO_4Si$ (M^+) 375.1866, found 375.1862

4-(1-Hydroxyethylidene)-2-(4-methoxybenzyl)-4*H*-isoquinoline-1,3-dione (8j) White solid; mp 140-141 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.9 (s, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.29-7.36 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.24 (s, 2H), 3.76 (s, 3H), 2.62 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.0, 170.1, 163.1, 159.0, 133.7, 133.1, 130.5 (2×C), 129.4, 129.1, 125.3, 124.0, 122.8, 113.7 (2×C), 100.0, 55.2, 42.9, 25.3. **EI-MS** *m/z* 323 (M^+); **EI-HRMS** calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158, found 323.1154.

2-(4-Chlorobenzyl)-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8k) White solid; mp 152-153 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.7 (s, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.57-7.61 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.31-7.37 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 2H), 2.62 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.2, 170.0, 163.1, 135.3, 133.7, 133.4, 133.2 (2×C), 130.4, 129.5 (2×C), 128.5, 125.4, 124.1, 122.6, 100.0, 42.8, 25.2. **EI-MS** *m/z* 327 (M^+); **EI-HRMS** calcd for $C_{18}H_{14}NO_3Cl$ (M^+) 327.0662, found 327.0670.

2-Benzyl-4-(1-hydroxyethylidene)-7-methoxy-4*H*-isoquinoline-1,3-dione (8l) White solid; mp 149-150 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.6 (s, 1H), 7.81 (d, *J* = 3.0 Hz, 1H), 7.53 (d, *J* = 9.3 Hz, 1H), 7.47 (d, *J* = 6.6 Hz, 2H), 7.18-7.33 (m, 4H), 5.31 (s, 2H), 3.88 (s, 3H), 2.59 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 181.5, 169.9, 163.0, 157.2, 136.8, 128.7 (2×C), 128.4 (2×C), 127.5, 127.0, 125.6, 123.9, 122.1, 110.7, 99.9, 55.6, 43.6, 25.1. **EI-MS** *m/z* 323 (M^+); **EI-HRMS** calcd for $C_{19}H_{17}NO_4$ (M^+) 323.1158, found 323.1146.

2-Benzyl-7-chloro-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8m) White solid; mp 142-143 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 16.8 (s, 1H), 8.31 (s, 1H), 7.53 (d, *J* = 1.2 Hz, 2H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.25-7.33 (m, 3H), 5.30 (s, 2H), 2.61(s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 183.5, 169.9, 162.1, 136.6, 133.2, 132.2, 131.4, 129.0, 128.9 (2×C), 128.5 (2×C), 127.7, 125.5, 124.1, 99.5, 43.7, 25.4. **EI-MS** *m/z* 327 (M^+); **EI-HRMS** calcd for $C_{18}H_{14}NO_3Cl$ (M^+) 327.0662, found 327.0660

2-Benzyl-6-chloro-4-(1-hydroxyethylidene)-4*H*-isoquinoline-1,3-dione (8n) White solid; mp 173-174 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ 17.0 (s, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.26-7.33 (m, 4H), 5.29 (s, 2H), 2.64(s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 184.2, 170.1, 162.4, 139.8, 136.6, 135.2, 131.1, 128.8, 128.4 (2×C), 127.6 (2×C), 125.7, 123.8, 121.0, 99.3, 43.6, 25.4. **EI-MS** *m/z* 327 (M^+); **EI-HRMS** calcd for $C_{18}H_{14}NO_3Cl$ (M^+) 327.0662, found 327.0660.

2-Benzyl-3-hydroxy-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid methyl ester (9) White solid; mp 138-139 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ Enol form: 15.89 (s, 1H), 8.40 (m, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.25-7.31 (m, 4H), 5.41 (s, 2H), 4.05 (s, 3H); Keto form: 8.23 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.25-7.31 (m, 4H), 5.26 (d, *J* = 14.1 Hz, 1H), 5.15 (d, *J* = 14.1 Hz, 1H), 4.93 (s, 1H), 3.67 (s, 3H); **^{13}C NMR** (100.0 MHz, $CDCl_3$): δ 174.0, 164.1,

162.0, 136.4, 133.6, 128.7, 128.6, 128.5, 128.4 (2×C), 128.37, 127.6, 124.3, 124.1, 120.9, 84.7, 52.8, 44.7. **EI-MS** *m/z* 309 (M^+); **EI-HRMS** calcd for $C_{18}H_{15}NO_4$ (M^+) 309.1001, found 309.1003.

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