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**AN EFFICIENT ONE-POT SYNTHESIS OF  
4-HYDROXYISOQUINOLINE-1,3(2*H*,4*H*)-DIONES FROM  
*N*-ALKYLBENZAMIDES AND  $\alpha$ -KETO ESTERS**

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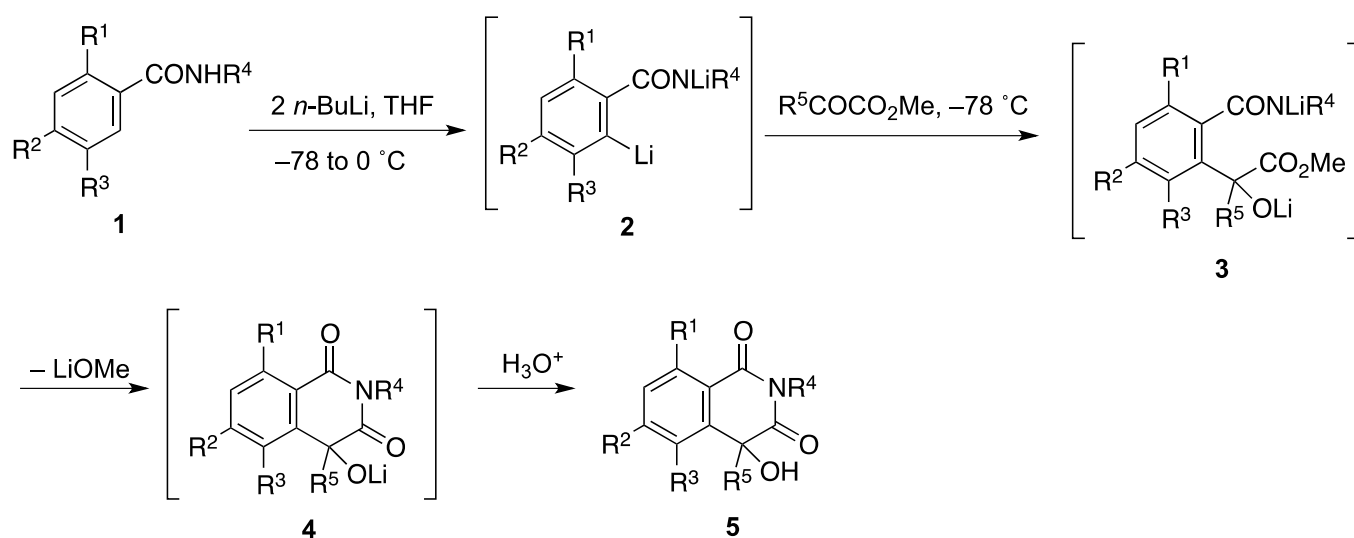
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**Abstract** – An efficient method for the preparation of 4-substituted 4-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones has been developed. Thus, treatment of *N*-alkyl-2,*N*-dilithiobenzamides, generated by treating *N*-alkylbenzamides with two equivalents of butyllithium, with methyl 2-oxoalkanoates resulted in the formation of the desired products in one pot in satisfactory yields.

The isoquinoline-1,3(2*H*,4*H*)-dione structure is often found in biologically active compounds.<sup>1</sup> Therefore, several new and efficient methods for the preparation of this class of heterocycles have recently been reported.<sup>2</sup> Although a few synthesis of 4-hydroxy derivatives, which are also of potential biological interest, have been reported,<sup>3</sup> there have been no methods for the general preparation of these derivatives. So, we were interested in developing an efficient approach for the general preparation of these derivatives. We, herein, report a convenient one-pot synthesis of 4-substituted 2-alkyl-4-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones (**5**) from *N*-alkylbenzamides (**1**). The method relies upon the reaction of *N*-alkyl-2,*N*-dilithiobenzamides (**2**),<sup>4</sup> generated from **1**, with  $\alpha$ -keto esters.

The one-pot preparation of **5** from **1** was conducted as illustrated in Scheme 1. The starting materials (**1**) were readily prepared from the respective benzoyl chlorides and primary amines according to the reported procedures (see Experimental). The first step of this synthetic method is the generation of dilithio compounds (**2**). After screening a range of conditions for the dilithiation of **1**, including solvents and reaction temperatures, we established that the treatment of **1** with two equivalents of butyllithium in THF at  $-78$  to  $0$  °C generated **2** efficiently. These were then allowed to react with methyl 2-oxoalkanoates at  $-78$  °C. Addition of the aryl anion of **2** to the carbonyl carbon of 2-oxoalkanoates followed by intramolecular lactamization of the resulting adducts (**3**) by the attack of the amide anion on the ester

carbonyl carbon giving the cyclization products (**4**) proceeded smoothly at this temperature. After aqueous work up and the subsequent purification of the crude products by column chromatography on silica gel or recrystallization, the desired products (**5**) were obtained.



The results obtained are summarized in Table 1. The bulkiness of the *N*-substituent of **1** affected the yields of the products. Thus, the reaction of *N*-methylbenzamide (**1a**) with methyl 2-phenyl-2-oxoacetate gave the corresponding product (**5a**) in 57% yield (Entry 1), while those using *N*-ethylbenzamide (**1b**) or *N*-(2-methoxyethyl)benzamide (**1c**) gave the corresponding products (**5b-i**) or (**5c**) in somewhat diminished 52 and 49% yield (Entries 2 and 4, respectively). With sterically crowded *N*-cyclopropylbenzamide (**1d**), the reaction resulted in the formation of rather complicated mixture of products and the yield of the desired product (**5d**) was 38% (Entry 5). The use of methyl pyruvate caused a considerable decrease in the yield of the desired product (**5b-ii**) (18%; Entry 3). This may be ascribed to the abstraction of an  $\alpha$ -hydrogen of methyl pyruvate with dilithio intermediate (**2b**). 2-Chloro-*N*-methylbenzamide (**1e**) worked well in the reaction with methyl 2-phenyl-2-oxoacetate to give the corresponding desired product (**5e**) in fair yield (Entry 6), but the use of 2-methoxy-*N*-methylbenzamide met with no success (Table 1 does not include this result). When 3-chloro- and 3-methoxy-benzamides (**1g**), (**1i**), and (**1j**) were used, the corresponding desired products (**5g**), (**5i-i**), (**5i-ii**), and (**5j**) were produced with highly regioselectivity; no another possible regioisomeric product was detected in each of the mixtures of these reactions (Entries 9, 11–13). These results indicate that lithiation took place only at the 2-position of the each amide, due to the adjacent orientation group. The yields of these products were relatively good, though that of **5g** was moderate, probably due to the formation of the corresponding benzyne derivative by elimination of the adjacent chloro group from the dilithio intermediate (**2g**).

**Table 1.** Preparation of 4-hydroxyisoquinoline-1,3(2*H*,4*H*)-diones (**5**)

Entry	<b>1</b>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup> in R <sup>5</sup> COCO <sub>2</sub> Me	<b>5</b>	Yield/% <sup>a</sup>
1	<b>1a</b>	H	H	H	Me	Ph	<b>5a</b>	57
2	<b>1b</b>	H	H	H	Et	Ph	<b>5b-i</b>	52
3	<b>1b</b>	H	H	H	Et	Me	<b>5b-ii</b>	18
4	<b>1c</b>	H	H	H	(CH <sub>2</sub> ) <sub>2</sub> OMe	Ph	<b>5c</b>	49
5	<b>1d</b>	H	H	H	<i>c</i> -Pr	Ph	<b>5d</b>	38
6	<b>1e</b>	Cl	H	H	Me	Ph	<b>5e</b>	68
7	<b>1f</b>	H	Cl	H	Me	Ph	<b>5f-i</b>	82
8	<b>1f</b>	H	Cl	H	Me	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>5f-ii</b>	69
9	<b>1g</b>	H	H	Cl	Me	Ph	<b>5g</b>	50
10	<b>1h</b>	H	OMe	H	Me	Ph	<b>5h</b>	48
11	<b>1i</b>	H	H	OMe	Me	Ph	<b>5i-i</b>	76
12	<b>1i</b>	H	H	OMe	Me	4-ClC <sub>6</sub> H <sub>4</sub>	<b>5i-ii</b>	74
13	<b>1j</b>	H	H	OMe	Et	Ph	<b>5j</b>	61

<sup>a</sup> Yields of isolated products.

In conclusion, we have developed an efficient synthetic method for 4-hydroxyisoquinoline-1,3(2*H*,4*H*)-dione derivatives, which would be difficult to prepare with conventional synthetic methods. Features of the present method are ready availability of the starting materials, simple manipulations, and avoidance of precious reagents. While some limitations have been noted with certain types of substrates and reactants, the present method may be of value in organic synthesis. Further applications of the dilithio compounds **2** to the synthesis of heterocyclic compounds are now investigating and the results will be reported elsewhere.

## EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin/Elmer Spectrum 65 FTIR spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a JEOL JMS-T100GCV spectrometer (EI TOF; 70eV). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF<sub>254</sub>. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

**Starting Materials.** *N*-Alkylbenzamides (**1b**),<sup>5</sup> (**1c**),<sup>6</sup> (**1d**),<sup>7</sup> (**1e**),<sup>8</sup> (**1f**),<sup>9</sup> (**1g**),<sup>10</sup> (**1h**),<sup>11</sup> (**1i**),<sup>12</sup> (**1j**),<sup>13</sup> methyl 2-(4-chlorophenyl)-2-oxoacetate,<sup>14</sup> and methyl 2-(4-methoxyphenyl)-2-oxoacetate<sup>15</sup> were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

**Typical Procedure for the Preparation of Isoquinoline-1,3(2*H*,4*H*)-diones (5). 4-Hydroxy-2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5a).** To a stirred solution of **1a** (0.14 g, 1.0 mmol) in THF (5 mL) at  $-78\text{ }^{\circ}\text{C}$  was added *n*-BuLi (1.6 M in hexane; 2.0 mmol) dropwise. The temperature was gradually raised to  $0\text{ }^{\circ}\text{C}$  and stirring was continued for 15 min at the same temperature. The mixture was cooled again to  $-78\text{ }^{\circ}\text{C}$  and PhCOCO<sub>2</sub>Me (0.16 g, 1.0 mmol) was added dropwise to it. After 5 min, saturated aqueous NH<sub>4</sub>Cl (15 mL) was added and the resulting mixture was extracted with AcOEt ( $3 \times 10$  mL). The combined extracts were washed with brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated by evaporation. The residue was purified by column chromatography on SiO<sub>2</sub> (AcOEt/hexane 1:3) to afford **5a** (0.15 g, 57%); a white solid; mp  $84\text{--}85\text{ }^{\circ}\text{C}$  (hexane); IR (KBr) 3454, 1722, 1674, 1605 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  3.35 (s, 3H), 4.53 (s, 1H), 7.21–7.29 (m, 5H), 7.51–7.54 (m, 1H), 7.65–7.68 (m, 2H), 8.23 (d,  $J = 7.4$  Hz, 1H); <sup>13</sup>C NMR  $\delta$  27.82, 75.81, 124.42, 124.86, 126.26, 128.31, 128.49, 128.75, 128.80, 134.52, 140.33, 142.51, 164.31, 176.00. HR-MS. Calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>3</sub> (M): 267.0895. Found:  $m/z$  267.0899. Anal. Calcd for C<sub>16</sub>H<sub>13</sub>NO<sub>3</sub>: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.67; H, 4.86; N, 5.16.

**2-Ethyl-4-hydroxy-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5b-i):** a colorless oil;  $R_f$  0.35 (AcOEt/hexane 1:7); IR (neat) 3453, 1721, 1671, 1603 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.14 (t,  $J = 7.4$  Hz, 3H), 3.90–3.97 (m, 1H), 4.01–4.08 (m, 1H), 4.52 (s, 1H), 7.21–7.29 (m, 5H), 7.51–7.55 (m, 1H), 7.66 (d,  $J = 8.0$  Hz, 2H), 8.24 (dd,  $J = 8.0, 1.1$  Hz, 1H); <sup>13</sup>C NMR  $\delta$  12.88, 36.46, 75.71, 124.64, 124.80, 126.15, 128.31, 128.45, 128.72, 128.76, 134.44, 140.24, 142.46, 163.81, 175.58. HR-MS. Calcd for C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub> (M): 281.1052. Found:  $m/z$  281.1063.

**2-Ethyl-4-hydroxy-4-methylisoquinoline-1,3(2*H*,4*H*)-dione (5b-ii):** a white solid; mp  $58\text{--}60\text{ }^{\circ}\text{C}$  (hexane); IR (KBr) 3362, 1719, 1671, 1606 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  1.24 (t,  $J = 7.4$  Hz, 3H), 1.66 (s, 3H), 3.75 (s, 1H), 3.96–4.03 (m, 1H), 4.06–4.13 (m, 1H), 7.49 (t,  $J = 7.4$  Hz, 1H), 7.68 (t,  $J = 7.4$  Hz, 1H), 7.76 (d,  $J = 7.4$  Hz, 1H), 8.16 (d,  $J = 7.4$  Hz, 1H); <sup>13</sup>C NMR  $\delta$  13.17, 34.63, 36.10, 72.11, 123.52, 124.59, 128.37, 128.59, 134.26, 141.90, 163.50, 177.40. HR-MS. Calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub> (M): 219.0895. Found:  $m/z$  219.0895.

**4-Hydroxy-2-(2-methoxyethyl)-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5c):** a colorless oil;  $R_f$  0.31 (AcOEt/hexane 1:4); IR (neat) 3451, 1724, 1675, 1603 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  3.14 (s, 3H), 3.47–3.55 (m, 2H), 4.10–4.18 (m, 1H), 4.21–4.26 (m, 1H), 4.53 (s, 1H), 7.27 (s, 5H), 7.50–7.54 (m, 1H), 7.64–7.66 (m, 2H), 8.22 (d,  $J = 8.0$  Hz, 1H); <sup>13</sup>C NMR  $\delta$  40.20, 58.58, 69.21, 75.86, 124.42, 124.90 (two overlapped Cs), 126.12, 128.41, 128.69 (two overlapped Cs), 134.51, 140.32, 142.57, 164.08, 175.86. HR-MS. Calcd for C<sub>18</sub>H<sub>17</sub>NO<sub>4</sub> (M): 311.1158. Found:  $m/z$  311.1146.

**2-Cyclopropyl-4-hydroxy-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5d):** a white solid; mp  $85\text{--}86\text{ }^{\circ}\text{C}$  (hexane); IR (KBr) 3453, 1732, 1681, 1604 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  0.12–0.16 (m, 1H), 0.62–0.67 (m, 1H),

0.90–0.96 (m, 1H), 1.10–1.16 (m, 1H), 2.76–2.78 (m, 1H), 4.63 (s, 1H), 7.13 (d,  $J = 7.4$  Hz, 2H), 7.26 (br s, 3H), 7.54 (t,  $J = 7.4$  Hz, 1H), 7.62–7.69 (m, 2H), 8.24 (d,  $J = 7.4$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  6.46, 9.22, 24.83, 76.35, 124.74, 124.87, 126.26, 128.28, 128.54, 128.72, 128.82, 134.55, 139.97, 141.74, 164.87, 177.23. HR-MS. Calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_3$  (M): 293.1052. Found:  $m/z$  293.1059. Anal. Calcd for  $\text{C}_{18}\text{H}_{15}\text{NO}_3$ : C, 73.71; H, 5.15; N, 4.78. Found: C, 73.42; H, 5.16; N, 4.75.

**8-Chloro-4-hydroxy-2-methyl-4-phenylisoquinoline-1,3(2H,4H)-dione (5e):** a white solid; mp 142–146 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3458, 1725, 1676  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.34 (s, 3H), 4.59 (s, 1H), 7.19 (dd,  $J = 7.4, 2.3$  Hz, 1H), 7.28–7.30 (m, 4H), 7.54–7.59 (m, 2H), 7.69 (dd,  $J = 6.3, 2.3$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  28.21, 75.81, 121.94, 124.95, 125.06, 128.78, 128.95, 132.37, 134.02, 135.24, 142.02, 142.71, 162.02, 174.75. HR-MS. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$  (M): 301.0506. Found:  $m/z$  301.0501. Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$ : C, 63.69; H, 4.01; N, 4.64. Found: C, 63.36; H, 4.00; N, 4.64.

**6-Chloro-4-hydroxy-2-methyl-4-phenylisoquinoline-1,3(2H,4H)-dione (5f-i):** a white solid; mp 162–165 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3483, 1718, 1661  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.35 (s, 3H), 4.51 (s, 1H), 7.21 (dd,  $J = 7.4, 1.1$  Hz, 2H), 7.29–7.31 (m, 3H), 7.49 (dd,  $J = 8.6, 1.1$  Hz, 1H), 7.64 (d,  $J = 1.1$  Hz, 1H), 8.17 (d,  $J = 8.6$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  27.92, 75.62, 122.80, 124.70, 126.51, 128.76, 128.98, 129.38, 129.90, 141.24, 141.86, 141.94, 163.54, 175.42. HR-MS. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$  (M): 301.0506. Found:  $m/z$  301.0507. Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$ : C, 63.69; H, 4.01; N, 4.64. Found: C, 63.29; H, 4.03; N, 4.58.

**6-Chloro-4-hydroxy-4-(4-methoxyphenyl)-2-methylisoquinoline-1,3(2H,4H)-dione (5f-ii):** a white solid; mp 145–147 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3454, 1723, 1677  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.32 (s, 3H), 3.75 (s, 3H), 4.5 (br, 1H), 6.80 (d,  $J = 9.2$  Hz, 2H), 7.10 (d,  $J = 9.2$  Hz, 2H), 7.49 (dd,  $J = 8.6, 2.3$  Hz, 1H), 7.65 (d,  $J = 2.3$  Hz, 1H), 8.15 (d,  $J = 8.6$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  27.89, 55.31, 75.32, 114.23, 122.81, 126.24, 126.47, 128.81, 129.29, 129.84, 141.17, 142.08, 159.77, 163.52, 175.62. HR-MS. Calcd for  $\text{C}_{17}\text{H}_{14}\text{ClNO}_4$  (M): 331.0611. Found:  $m/z$  331.0609. Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{ClNO}_4$ : C, 61.55; H, 4.25; N, 4.22. Found: C, 61.22; H, 4.38; N, 4.17.

**5-Chloro-4-hydroxy-2-methyl-4-phenylisoquinoline-1,3(2H,4H)-dione (5g):** a white solid; mp 162–164 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3479, 1718, 1661  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.34 (s, 3H), 4.65 (s, 1H), 7.26–7.35 (m, 5H), 7.51 (t,  $J = 8.0$  Hz, 1H), 7.65 (dd,  $J = 8.0, 1.1$  Hz, 1H), 8.30 (dd,  $J = 8.0, 1.1$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  28.18, 75.91, 125.24, 126.95, 127.57, 128.55, 128.66, 129.95, 133.87, 136.66, 137.27, 139.66, 163.09, 174.66. HR-MS. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$  (M): 301.0506. Found:  $m/z$  301.0509. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3$ : C, 63.69; H, 4.01; N, 4.64. Found: C, 63.50; H, 4.01; N, 4.54.

**4-Hydroxy-6-methoxy-2-methyl-4-phenylisoquinoline-1,3(2H,4H)-dione (5h):** a white solid; mp 119–122 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3435, 1716, 1663, 1604  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.32 (s, 3H), 3.85 (s,

3H), 4.58 (s, 1H), 7.02 (dd,  $J = 8.6, 2.3$  Hz, 1H), 7.08 (d,  $J = 2.3$  Hz, 1H), 7.23–7.30 (m, 5H), 8.17 (d,  $J = 8.6$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  27.69, 55.68, 75.87, 109.95, 115.82, 117.32, 124.80, 128.48, 128.77, 130.59, 142.48, 142.72, 163.90, 164.59, 176.06. HR-MS. Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_4$  (M): 297.1001. Found:  $m/z$  297.1000. Anal. Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_4$ : C, 68.68; H, 5.09; N, 4.71. Found: C, 68.36; H, 5.08; N, 4.68.

**4-Hydroxy-5-methoxy-2-methyl-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5i-i):** a white solid; mp 168–170 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3499, 1724, 1674  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.29 (s, 3H), 3.72 (s, 3H), 4.96 (s, 1H), 7.20 (d,  $J = 8.0$  Hz, 1H), 7.27–7.31 (m, 5H), 7.55 (t,  $J = 8.0$  Hz, 1H), 7.99 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  27.73, 56.37, 75.58, 117.07, 121.17 (two overlapped Cs), 125.22, 126.24, 128.32, 128.43, 130.07, 141.79, 156.46, 163.77, 172.37. HR-MS. Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_4$  (M): 297.1001. Found:  $m/z$  297.1017. Anal. Calcd for  $\text{C}_{17}\text{H}_{15}\text{NO}_4$ : C, 68.68; H, 5.09; N, 4.71. Found: C, 68.55; H, 5.16; N, 4.70.

**4-(4-Chlorophenyl)-4-hydroxy-5-methoxy-2-methylisoquinoline-1,3(2*H*,4*H*)-dione (5i-ii):** a white solid; mp 160–163 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3433, 1723, 1669  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  3.30 (s, 3H), 3.75 (s, 3H), 4.93 (s, 1H), 7.22 (d,  $J = 8.0$  Hz, 1H), 7.25 (s, 4H), 7.57 (t,  $J = 8.0$  Hz, 1H), 8.00 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  27.78, 56.36, 75.05, 117.00, 121.27, 126.12, 126.79, 127.79, 128.62, 130.36, 134.42, 140.46, 156.32, 163.56, 171.98. HR-MS. Calcd for  $\text{C}_{17}\text{H}_{14}\text{ClNO}_4$  (M): 331.0611. Found:  $m/z$  331.0605. Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{ClNO}_4$ : C, 61.55; H, 4.25; N, 4.22. Found: C, 61.22; H, 4.28; N, 4.15.

**2-Ethyl-4-hydroxy-5-methoxy-4-phenylisoquinoline-1,3(2*H*,4*H*)-dione (5j):** a white solid; mp 119–122 °C (hexane/ $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3484, 1725, 1674  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  1.11 (t,  $J = 6.9$  Hz, 3H), 3.72 (s, 3H), 3.85–3.91 (m, 1H), 3.97–4.04 (m, 1H), 4.97 (s, 1H), 7.19 (d,  $J = 8.0$  Hz, 1H), 7.27–7.30 (m, 5H), 7.55 (t,  $J = 8.0$  Hz, 1H), 7.99 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  12.82, 36.28, 56.39, 75.56, 117.03, 121.19 (two overlapped Cs), 125.16, 126.45, 128.27, 128.40, 130.01, 141.77, 156.47, 163.25, 172.00. HR-MS. Calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}_4$  (M): 311.1158. Found:  $m/z$  311.1154. Anal. Calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}_4$ : C, 69.44; H, 5.50; N, 4.50. Found: C, 69.37; H, 5.59; N, 4.49.

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## REFERENCES

- (a) H.-R. Tsou, M. Otteng, T. Tran, M. B. Floyd, Jr., M. Reich, G. Birnberg, K. Kutterer, S. Ayral-Kaloustian, M. Ravi, R. Nilakantan, M. Grillo, J. P. McGinnis, and S. K. Rabindran, *J. Med. Chem.*, 2008, **51**, 3507; (b) H.-R. Tsou, X. Liu, G. Birnberg, J. Kapran, M. Otteng, T. Tran, K. Kutterer, Z. Tang, R. Suayanm, M. Ravi, A. Bretz, M. Grillo, J. P. McGinnis, S. K. Rabindran, S.

- Ayral-Kaloustian, and T. S. Mansour, *J. Med. Chem.*, 2009, **52**, 2289; (c) X.-Y. Lu, Y.-D. Chen, N.-y. Sun, Y.-J. Jiang, and Q.-D. You, *J. Mol. Model.*, 2010, **16**, 163; (d) M. Billamboz, F. Bailly, C. Lion, N. Touati, H. Vezin, C. Calmels, M.-L. Andréola, F. Christ, Z. Debyser, and P. Cotelle, *J. Med. Chem.*, 2011, **54**, 1812.
2. (a) W. Zhao, P. Xie, M. Zhang, B. Niu, Z. Bian, C. Pittman, and A. Zhou, *Org. Biomol. Chem.*, 2014, **12**, 7690; (b) M. Zhang, P. Xie, W. Zhao, B. Niu, W. Wu, Z. Bian, C. U. Pittman, Jr., and A. Zhou, *J. Org. Chem.*, 2015, **80**, 4176; (c) S. Tang, Y.-L. Deng, J. Li, W.-X. Wang, G.-L. Ding, M.-W. Wang, Z.-P. Xiao, Y.-C. Wang, and R.-L. Sheng, *J. Org. Chem.*, 2015, **80**, 12599; (d) P. Qian, B. Du, W. Jiao, H. Mei, J. Han, and Y. Pan, *Beilstein J. Org. Chem.*, 2016, **12**, 301; (e) D. Yuan, Z. Duan, Y. Rao, and M.-W. Ding, *Tetrahedron*, 2016, **72**, 338; (f) A. S. Harisha, S. P. Hayak, K. Nagarajan, T. N. G. Row, and A. A. Hosamani, *Tetrahedron*, 2016, **72**, 2880; (g) X. Liu, T. Cong, P. Liu, and P. Sun, *Tetrahedron*, 2016, **14**, 9416; (h) S.-L. Zhu, P.-X. Zhou, and X.-F. Xia, *RSC Adv.*, 2016, **6**, 63325.
  3. (a) R. Suau and E. P. de Inestrosa Villatoro, *Tetrahedron*, 1994, **50**, 4987; (b) H. Heaney and M. O. Taha, *ARKIVOC*, 2000, **iii**, 343.
  4. (a) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 853; (b) T. M. Bare, C. W. Draper, C. D. McLaren, L. M. Pullan, J. Patel, and J. B. Patel, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 55; (c) B. W. Trotter, K. K. Nanda, N. R. Kett, C. P. Legan, J. J. Lynch, G. L. Stump, L. Kiss, J. Wang, R. H. Spencer, S. A. Kane, R. B. White, R. Zhang, D. Kenneth, N. J. Liverton, C. J. McIntyre, D. C. Beshore, G. D. Hartman, and C. J. Dinsmore, *J. Med. Chem.*, 2006, **49**, 6954; (d) M. R. Rao, S. Johnson, and D. F. Perepichka, *Org. Lett.*, 2016, **18**, 3574.
  5. A. Koziara, S. Zawadzki, and A. Zwierzak, *Synthesis*, 1979, 527.
  6. G. Pelletier, W. S. Bechara, and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 12817.
  7. V. C. Agwada, *J. Chem. Eng. Data*, 1984, **29**, 231.
  8. J. F. Galan, J. Brown, J. L. Wildin, Z. Liu, D. Liu, G. Moyna, and V. Pophristic, *J. Phys. Chem. B*, 2009, **113**, 12809.
  9. M. R. Banks and R. F. Hudson, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1211.
  10. M. Kuriyama, N. Hamaguchi, G. Yano, K. Tsukuda, K. Sato, and O. Onomura, *J. Org. Chem.*, 2016, **81**, 8934.
  11. T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565.
  12. L. G. Czaplewski, I. Collins, E. A. Boyd, D. Brown, S. P. East, M. Gardiner, R. Fletcher, D. J. Haydon, V. Henstock, P. Ingram, C. Jones, C. Noula, L. Kennison, C. Rockley, V. Rose, H. B. Thomaidis-Brears, R. Ure, M. Whittaker, and N. R. Stokes, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 524.

13. P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 1964, 924.
14. J. A. Turner, [\*J. Org. Chem.\*, 1983, \*\*48\*\*, 3401.](#)
15. Y. Mizutani, H. Tanimoto, T. Morimoto, Y. Nishiyama, and K. Kakiuchi, [\*Tetrahedron Lett.\*, 2012, \*\*53\*\*, 5903.](#)