An Efficient Synthetic Route to Ethyl 2-Aryl-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates[1]

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Certain 2-aryl-1,3(2*H*,4*H*)-dioxoisoquinolines are known as herbicides and plant growth regulators (PGR's).[2] In herbicide screens many of these compounds caused agravitropic behavior of the roots of several test species, a phenotype characteristic of inhibitors of auxin transport. Most auxin transport inhibitors bind to a specific site on the plant plasma membrane, which is defined by its affinity for the herbicide *N*-1-naphthylphthalamic acid (NPA).[3,4a] On the basis of these observations we carried out *in vivo* and *in vitro* studies and concluded that the mode of action of these aryldioxoisoquinolines is the inhibition of auxin transport.[5a] This activity might be a function of (1) binding of the parent molecule to the NPA receptor, (2) the propensity toward metabolic ring-opening, yielding more traditional phthalamic acid analogues, and (3) binding of the metabolite to the receptor.[5]

With this knowledge in hand, we pursued a series of target compounds **5a**−**j** (Table 1) as novel auxin transport inhibitors which proved to be of considerable utility for the production of hybrid seed as well as for crop yield enhancement. Thus, molecular modeling and topological comparisons of a lead compound, 2-[*p*-(ethoxycarbonyl)-phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline (**2b**), with NPA, DPX-1840 and its ring-opened metabolite,[4b] morphactin (chlorflurenol[4a]), and related auxin transport inhibitors[2,4,5] (Scheme 1) led us to design and synthesize the title compounds. Furthermore, the judicious selection and placement of aromatic and requisite orthogonal acidic functionality[5b,c] were based upon known[4,5] and in-house structure−activity relationships (SAR) in such families. The 2-aryl substituents in our final targets were chosen by consideration of the above literature precedents along with the desire to explore a range of molecular parameters, such as size and lipophilicity. Herein, we report an efficient synthetic strategy to 10 such examples, several of which have expressed high levels of PGR activity.

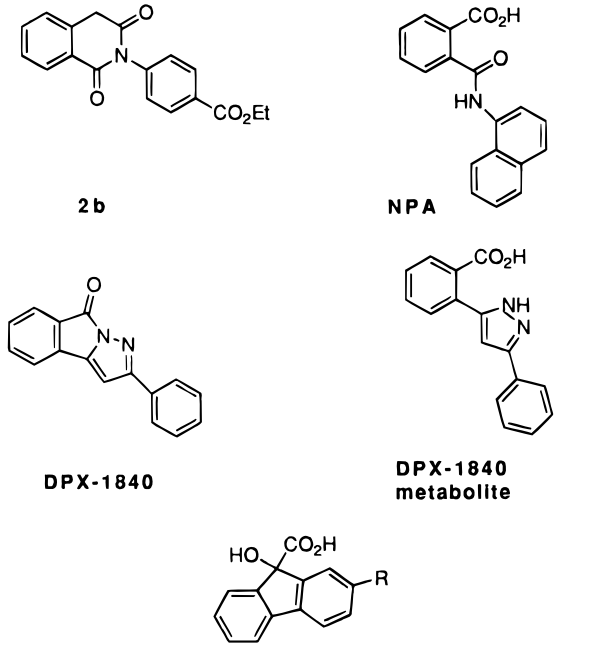
The 2-aryl-1,3(2*H*,4*H*)-dioxoisoquinoline intermediates **2a**−**j** were prepared in 49−85% yield in a conventional manner by condensation of homophthalic anhydride with the appropriate aniline derivative **1a**−**j** in azeotropically refluxing xylene[5,6] (Scheme 2). It is of interest to note that the lipophilic aniline used to prepare **2h** was obtained in 35% yield by H_2SO_4-catalyzed alkylation of *m*-toluidine with 2-propanol[7] or in ca. 60% yield by $AlCl_3$-catalyzed Friedel−Crafts alkylation with isopropyl chloride.[8] Aryl substituents and yields for the intermediates **2a**−**j, 3a**−**j, and 4a**−**j** and final targets **5a**−**j** are compiled in Table 1.

Table 1. Substituents and Yields of Intermediates 2a−j, 3a−j, 4a−j and Products 5a−j

				% yield			
entry	R_1	R_2	R_3	**2**	**3**, method[a]	**4**	**5**
a	H	H	H	85	A, 51	89	54
b	H	CO_2Et	H	80	A, 53; B, 57	92	45
c	H	Cl	H	68	A, 43	92	51
d	Cl	H	Cl	74	A, 47; B, 60	89	52
e	MeO	H	MeO	53	A, 30; B, 76	75	47
f	H	Me	H	78	A, 49	72	49
g	Me	H	H	52	A, 26	50	46
h	Me	iPr	H	80	B, 64	85	61
i	H	iPr	H	80	B, 45	78	38
j	CF_3	H	CF_3	49	B, 62	63	49

[a] Method A: EtOCOCl, pyridine. Method B: NaH, PhNCO followed by EtOH, reflux.

Scheme 1. Examples of Modern Auxin Transport Inhibitors with PGR Activity



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(1) This paper is dedicated to the memory of Geraldine C. Semple.

(2) D'Amico, J. J. (Monsanto Co.). U.S. Patent 4097260, 1978.
(3) Thomson, K. S.; Hertel, R.; Mueller, S.; Tavares, J. E. *Planta* **1973**, *109*, 337.
(4) (a) Bures, M. G.; Black-Schaefer, C.; Gardner, G. *J. Comput.-Aided Mol. Des.* **1991**, *5*, 323. (b) Beyer, E. M.; Sweetser, A. L. *Plant Physiol.* **1976**, *57*, 839.
(5) (a) Gardner, G.; Semple, J. E. *J. Plant Growth Regul.* **1990**, *9*, 161. (b) Katekar, G. F. *Phytochemistry* **1976**, *15*, 1421. (c) Gardner, G.; Sanborn, J. R. *Plant Physiol.* **1989**, *90*, 291.
(6) (a) Cheng, C.-Y.; Tsai, H.-B.; Lin, M.-S. *J. Heterocycl. Chem.* **1995**, *32*, 73. (b) Murthy, A. R. K.; Chapman, J. M.; Wyrick, S. D.; Hall, I. H. *Pharm. Res.* **1986**, *3*, 286. (c) The condensations may also be conveniently carried out in toluene or acetic acid at reflux. The addition of 0.1−0.3 mol equiv of DBU or triethylamine catalyzes the reaction in the aromatic hydrocarbon solvents.
(7) (a) Private communication from R. J. G. Searle, Shell Research Limited, Sittingbourne Research Centre, Sittingbourne, Kent, U.K. (b) Gilkerson, T. (Shell Internationale Research Maatschappij B.V. Neth.). Neth. Appl., NL 8006568, 1981. (c) Koval'skaya, S. S.; Kozlov, N. G.; Shavyrin, S. V. *Khim. Prir. Soedin.* **1991**, 29; *Chem. Abstr.* **1992**, *116*, 129270. (d) Burmistrov, S. I. *Zh. Obsch. Khim.* **1965**, *1*, 1838.
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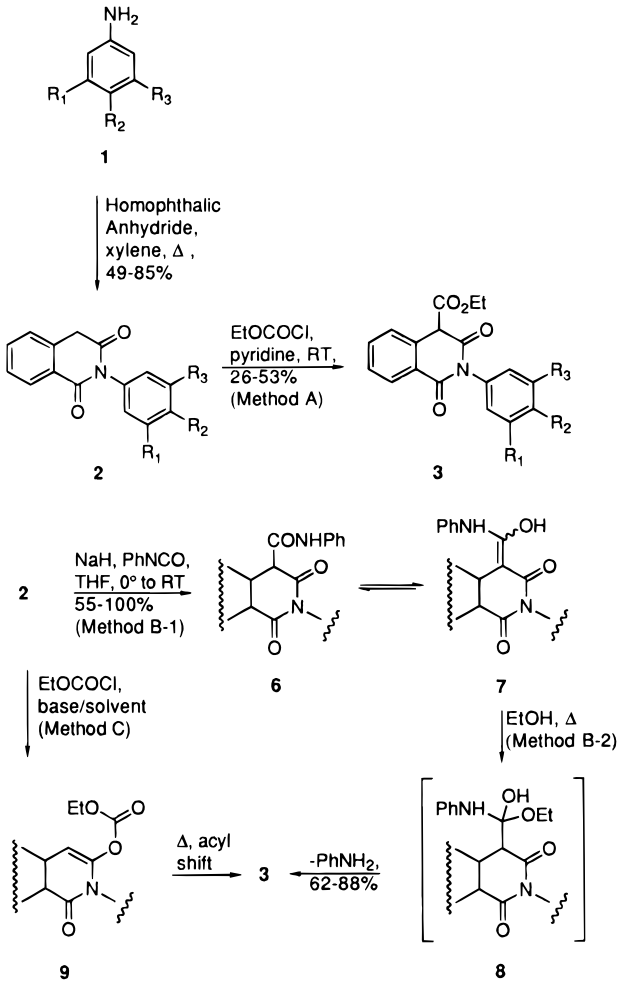
Scheme 2



C-4 ethoxycarbonylation of **2a**−**j** could be effected by three complementary methods. The initial one-step method consisted of acylation with ethyl chloroformate in pyridine[9] and afforded **3a**−**g** in 26−53% yield (Table 1, method A). An indirect but significantly improved two-step protocol was developed based on the work of Kadin.[10] Thus, C-4 enolate formation and reaction with phenyl isocyanate afforded the *N*-phenylcarboxamides **6b,d,e,h**−**j**. In our hands, use of sodium hydride as base gave consistently superior yields of product over the triethylamine method employed by Kadin in his work. Alcoholysis of **6b,d,e,h**−**j** in refluxing ethanol under neutral conditions delivered the corresponding ethyl esters **3b,d,e,h**−**j** in overall yields of 45−76% from **2b,d,e,h**−**j** (Table 1, method B). A plausible mechanism for this latter transformation may involve an addition−elimination process via the enol-form **7** leading to intermediate **8**. Subsequent loss of aniline affords the ester product **3**. This neutral alcoholysis method is not limited to the preparation of ethyl esters and indeed, as reported by Kadin, is applicable to the synthesis of a wide range of straight- or branched-chain C_1−C_6 ester derivatives.[10b,c]

We briefly investigated another approach to **3c,d** which entailed initial enolate O-acylation with ethyl chloroformate followed by a 1,3-O- to C-acyl shift process (method C).[11] Enolate formation with sodium hydride or LDA under standard conditions and subsequent trapping with the above electrophile afforded modest yields of carbonate derivatives **9c,d** along with recovered starting material. Operationally, it was more convenient and efficient to use triethylamine in THF or anhydrous potassium carbonate in DMF as the base/solvent pairs where essentially quantitative yields of **9c,d** could be realized. Unfortunately, thermally induced 1,3-acyl shift of **9d** at 30−60 °C in DMF produced **3d** in only 14−35% yield. Addition of DMAP[12] did little to alter the course of the reaction, while other solvents were less satisfactory.

Our initial attempts to install the α-hydroxy group by direct oxygenation[13] of the enolate derived from **3a** using various bases, dry oxygen, and reductive workup conditions led to a complex mixture of products containing the 1,3,4-trione byproducts **10a**.[14] Although the MoOPH protocol[15] might have succeeded with our substrates, we were concerned about handling and disposal of the HMPA produced from this reagent. On the basis of the precedent of Lawesson and Gronwall,[16] the α-hydroxy group was introduced indirectly by an efficient two-step process. Treatment of the sodium enolate of **3a**−**j** with benzoyl peroxide at 0 °C to room temperature afforded the α-benzoyloxy ester derivatives **4a**−**j** in 70−92% yield (Scheme 3). Finally, selective alcoholysis of the benzoyl moiety was effected by treatment of **4a**−**j** with 6−10 equiv of sodium ethoxide at 0 °C and produced the desired α-hydroxy ester derivatives **5a**−**j** in 38−54% yield. In addition to very minor amounts of the expected alkoxide-derived ring-opened amide−ester byproducts, the predominant byproducts produced during the hydrolysis stage proved to be the 1,3,4-trione derivatives **10**, which were also detected during the attempted direct oxygenation protocol discussed above.[14]

Several of the targets prepared herein expressed potent auxin transport inhibition activity in selected *in vitro* assays. Furthermore, when field tested in Europe, certain members of this class demonstrated interesting levels of PGR activity for the production of hybrid wheat

(9) (a) Ethoxycarbonylation of homophthalic anhydride derivatives with this system is known. However, we are unaware of any reports describing the direct acylation of 1,3(2H, 4H)-dioxoisoquinolines (homophthalimides) **2** by this method, cf.: (b) Chatterjea, J. N.; Mukherjee, S. K.; Bhakta, H. C. J.; Zilliken, F. *Chem. Ber.* **1980**, *113*, 3927. (c) Hellou, J.; Kingston, J. F.; Fallis, A. G. *Synthesis* **1984**, 1014. (d) Schnekenburger, J. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1965**, *298*, 715.

(10) (a) Kadin, S. (Pfizer, Inc.). U.S. Patent 4569942, 1986. (b) Kadin, S. (Pfizer, Inc.). U.S. Patent 3998954, 1976. (c) Kadin, S. *J. Org. Chem.* **1969**, *34*, 3178. (d) For application of this protocol to antinflammatory 1-acyl-2-oxindole-3-carboxamides, see: Kadin, S. (Pfizer Co.). U.S. Patent 4730004, 1988.

(11) To the best of our knowledge, there exists no literature precedent for the 1,3-O- to C-acyl shift in the subject isoquinolinedione systems. However, similar acyl shifts have been successfully executed in a variety of other systems; cf.: (a) Lu, J. Q.; Wang, S. Y.; Zhang, P. *Chin. Chem. Lett.* **1992**, *3*, 337. (b) Oliver, J. E.; Wilzer, K. R.; Waters, R. M. *Synthesis* **1990**, 1117. (c) Winkler, D. A.; Liepa, A. J.; Anderson-McKay, J. E.; Hart, N. K. *Pestic. Sci.* **1989**, *27*, 45. (d) For examples of the synthesis and O- to C-acyl shifts of enol esters to *β*-keto esters, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; pp 743−744. (e) Seminal O-acylation and O- to C-acyl migration studies: Eisenhauer, H. R.; Link, K. P. *J. Am. Chem. Soc.* **1953**, *75*, 2044

(12) Scriven, F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

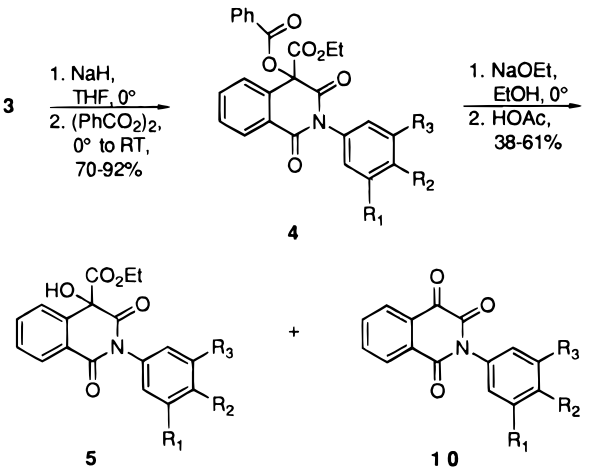
(13) (a) Wasserman, H. H.; Lipshutz, B. *Tetrahedron Lett.* **1977**, 4595. (b) For an excellent compilation of references on the subject of enolate hydroxylation, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; pp 488−490.

(14) 2-Aryl-1,3,4-(2*H*)-trioxoisoquinolines, also known as phthalonimides, have been previously described; see: (a) Peterson, S.; Heitzer, H. *Liebigs Ann. Chem.* **1978**, 283. (b) Buu-Hoi, N. P.; Saint-Ruf, G.; Bourgeade, J. C. *J. Heterocycl. Chem.* **1968**, *5*, 545. (c) Meyer, A.; Villenet, R. *C. R. Hebd. Seances Acad. Sci.* **1931**, *193*, 531, 1095.

(15) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (b) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. See also ref 13b.

(16) Lawesson, S. O.; Gronwall, S. *Acta Chem. Scand.* **1960**, *14*, 1445.

Scheme 3



seed as well as for crop yield enhancement in soybeans, sugar beets, and cotton. Complete SAR and biological results will be described in a forthcoming publication.

In conclusion, we have prepared a series of 10 novel ethyl 2-aryl-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates **5a**−**j** possessing different *N*-phenyl substituents by a convenient four- or five-step protocol. Especially noteworthy of this new methodology is the unconventional introduction of the C-4 ester moiety via neutral alcoholysis of the phenylcarboxamide precursor **6b,d,e,h**−**j** as well as the indirect α-hydroxylation of an activated tertiary center using a benzoyloxyation/hydrolysis strategy. These are both somewhat uncommon yet mild and potentially useful processes which may find further application in organic synthesis.

Experimental Section

^{1}H-NMR spectra were obtained on spectrometers operating at 60 and 300 MHz. All melting points are uncorrected and are reported in degrees centigrade (°C). The elemental microanalyses and low-resolution mass spectral acquisitions were performed by the Shell BSRC Analytical Chemistry Department. Thin layer chromatography was performed using Merck silica gel 60 F-254 plates. Visualization was effected with UV and/or phosphomolybdic acid. All reactions were run under a positive pressure of nitrogen. All solvents were anhydrous and were used as purchased from Aldrich. All reagents were purchased from Aldrich.

General Procedure for the Synthesis of 2-Aryl-1,3-(2*H*,4*H*)-dioxoisoquinolines 2a−**j.** A mixture of homophthalic anhydride (16.21 g, 0.10 mol) and the appropriate aniline derivative (0.11 mol) in 250 mL of xylene was rapidly stirred and azeotropically heated at reflux using a Dean−Stark trap for 4−72 h until water evolution ceased and TLC monitoring (hexanes/ethyl acetate/THF, 4/1/1 to 2/1/1 mixtures) suggested completion of the reaction. The solvent was removed, and the residue was purified either by recrystallization from 2-propanol, ethanol, methanol, or ethyl acetate/hexane mixtures or by flash chromatography using ethyl acetate, hexane or ethyl acetate/methylene chloride gradient systems to afford the products **2a**−**j** as nearly colorless solids. Range of principal IR bands for **2a**−**j** in KBr: 1705−1715, 1665−1670, 1590−1595 cm^{-1}.

2-Phenyl-1,3(2*H*,4*H*)-dioxoisoquinoline (2a): mp 188−189 °C, lit.[6b] mp 181−184 °C; lit.[17] mp 190−192 °C; yield 87%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 4.20 (s, 2H), 7.04−8.25 (m, 9H). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.25; H, 4.40; N, 6.00.

2-[4-(Ethoxycarbonyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline (2b): mp 170−172 °C; yield 80%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.35 (t, J = 7 Hz, 3H), 4.10 (s, 2H), 4.36 (q, J = 7 Hz, 2H), 6.95−8.15 (m, 8H); MS (EI) 309 au. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.20; H, 4.80; N, 4.73.

2-(4-Chlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2c): mp 176−177.5 °C; lit.[6b] mp 166−168 °C; yield 68%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 4.23 (s, 2H), 7.0−8.10 (m, 8H). Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C, 66.65; H, 3.80; N, 5.13.

2-(3,5-Dichlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2d): mp 230.5−232.5 °C, lit.[2] mp 241 °C; yield 74%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 4.18 (s, 2H), 7.32−7.7 (m, 5H), 8.15 (m, 1H), 8.42 (d, J = 8.0 Hz, 1H); MS (EI) 305, 307 au. Anal. Calcd for $C_{15}H_9Cl_2NO_2$: C, 58.85; H, 2.96; N, 4.58. Found: C, 58.55; H, 2.90; N, 4.82.

2-(3,5-Dimethoxyphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2e): mp 178−179.5 °C, lit.[2] mp 145−146 °C; yield 64%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.71 (s, 6H), 4.10 (s, 2H), 6.42 (m, 2H), 6.63 (m, 1H), 7.13−7.55 (m, 3H), 8.0 (m, 1H); MS (EI) 297 au. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 69.03; H, 5.11; N, 4.82.

2-(4-Methylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2f): mp 170.5−172.5 °C, lit.[6b] mp 166−168 °C; yield 78%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 2.50 (s, 3H), 4.15 (s, 2H), 7.0−7.95 (m, 8H); MS (EI) 251 au. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.80; H, 5.22; N, 5.63.

2-(3-Methylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2g): mp 111.5−113.5 °C, lit.[6b] mp 108−110 °C; yield 52%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.12 (s, 2H), 7.0−7.9 (m, 8 H); MS (EI) 251 au. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.85; H, 5.38; N, 5.51.

2-(3-Methyl-4-isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2h): mp 158−160 °C; yield 80%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 6H), 2.30 (s, 3H), 3.10 (m, 1H), 4.12 (s, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.25−7.8 (m, 6H); MS (EI) 293 au. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.61; H, 6.63; N, 4.84.

2-(4-Isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline (2i): mp 172−174 °C; yield 82%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 6H), 3.10 (m, 1H), 4.14 (s, 2H), 7.17 (d, 1H, J = 8.0 Hz), 7.25−7.8 (m, 7H); MS (EI) 279 au. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.38; H, 6.10; N, 5.03.

2-[3,5-Bis(trifluoromethyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline (2j): mp 203−205 °C; lit.[2] mp 205−206 °C; yield 49%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 4.10 (s, 2H), 7.2−7.8 (m, 7H); MS (EI) 373 au. Anal. Calcd for $C_{17}H_9F_6NO_2$: C, 54.70; H, 2.43; N, 3.75. Found: C, 55.01; H, 2.65; N, 4.01.

General Procedure for the Ethoxycarbonylation of 2a−**g. Synthesis of Ethyl 2-Aryl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates 3a**−**g. Method A.** To a solution of **2a**−**g** (0.020 mol) in 50 mL of anhydrous pyridine was added ethyl chloroformate (3.26 g, 0.030 mol, 2.90 mL) rapidly dropwise over 5 min. The mixture was stirred at ambient temperature for 16−24 h. If TLC analysis (ethyl acetate/hexane mixtures) indicated the presence of unreacted starting material, an additional portion of ethyl chloroformate was added (generally 0.326 g, 0.0030 mol, 0.29 mL was sufficient to complete the reaction). After completion of the reaction, the mixture was poured into an ice-cold solution of acetic acid (45 mL) and water (150 mL). After stirring for 20 min at 0 °C, the resultant solid was collected by suction filtration, washed with ice/water, dried, and recrystallized from ethanol/acetone mixtures to afford the following products **3a**−**g** as nearly colorless, tiny needles. Range of principal IR bands for **3a**−**g** in KBr: ∼3400 (br), 2965−2975, 1660−1700, 1600−1615, 1575−1595 cm^{-1}.

Ethyl 2-phenyl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3a): mp 155−157 °C; yield 51%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.50 (t, J = 7 Hz, 3H), 4.53 (q, J = 7 Hz, 2H), 7.10−8.60 (m, 9H); MS (EI) 309 au. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.25; H, 4.90; N, 4.55.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3b): mp 175−177 °C; yield 53%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.40 (t, J = 7 Hz, 3H), 1.53 (t, J = 7 Hz, 3H), 4.41 (q, J = 7 Hz, 2H), 4.55 (q, J = 7 Hz, 2H), 7.25−8.6 (m, 8H); MS (EI): 381 au. Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 66.25; H, 5.00; N, 3.73.

(17) (a) Modi, A. R.; Usgaonkar, R. N. *Indian J. Chem.* **1979**, *18B*, 304. (b) Gerald, R.; Popp, F. *J. Heterocycl. Chem.* **1969**, *6*, 12.

Ethyl 2-(4-chlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3c): mp 174−176 °C; yield 43%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.52 (t, J = 7 Hz, 3H), 4.52 (q, J = 7 Hz, 2H), 7.0−8.6 (m, 8H); MS (EI) 342, 344 au. Anal. Calcd for $C_{18}H_{14}ClNO_4$: C, 62.89; H, 4.10; N, 4.07. Found: C, 63.25; H, 4.13; N, 4.10.

Ethyl 2-(3,5-dichlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3d): mp 191−193 °C; yield 47%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.19 + 1.44 (2t, J = 7.0 Hz, 3H), 4.23 + 4.53 (2q, J = 7 Hz, 2H), 5.41 (s, ∼1H, C-4 methine), 7.37−7.85 (m, 5H), 8.17 (m, 1H), 8.52 (d, J = 8.2 Hz, 1H); MS (EI) 377, 379 au. Anal. Calcd for $C_{18}H_{13}Cl_2NO_4$: C, 57.16; H, 3.46; N, 3.70. Found: C, 56.77; H, 3.39; N, 3.61.

Ethyl 2-(3,5-dimethoxyphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3e): mp 161−163 °C; yield 52%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.40 (t, J = 7.0 Hz, 3H), 3.70 (s, 6H), 4.50 (q, J = 7 Hz, 2H), 7.40−7.65 (m, 5H), 7.95 (m, 1H), 8.45 (d, J = 8.2 Hz, 1H); MS (EI) 369 au. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.37; H, 5.09; N, 4.01.

Ethyl 2-(4-methylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3f): mp 164−166 °C; yield 56%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 + 1.55 (2t, J = 7.0 Hz, 3H), 2.40 + 2.50 (2s, 3H), 4.25 + 4.55 (2q, J = 7.0 Hz, 2H), 7.12−7.84 (m, 6H), 7.95 (m, 1H), 8.40 (dd, J = 8.2, 2.1 Hz, 1H), 8.55 (dd, J = 8.2, 2.1 Hz, 1H); MS (EI) 323 au. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.67; H, 5.65; N, 4.29.

Ethyl 2-(3-methylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3g): mp 130−132 °C; yield 26%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 + 1.55 (2t, J = 7.0 Hz, 3H), 2.40 (s, 3H), 4.24 + 4.54 (2 q, J = 7.0 Hz, 2H), 7.00−7.82 (m, 6H), 7.95 (m, 1H), 8.42 (dd, J = 7.4, 2.0 Hz, 1H), 8.58 (dd, J = 7.4, 2.0 Hz, 1H); MS (EI) 323 au. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.46; H, 5.46; N, 4.51.

Synthesis of Ethyl 2-Aryl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates 3b,d,e,h−j via Alcoholysis of the C-4 *N*-Phenylcarboxamide Derivatives 6b,d,e,h−j. Method B-1. General Procedure for the Synthesis of the *N*-Phenylcarboxamide Derivatives 6b,d,e,h−j. To a suspension of sodium hydride (0.26 g, 0.011 mol, from 0.44 g of 60% dispersion in oil, washed three times with dry hexane) in 50 mL of anhydrous THF at 0 °C was added with good stirring a solution of **2b,d,e,h−j** (0.010 mol) in 50 mL of dry THF over about 30 min. After 15 min, the solution was briefly warmed to ambient temperature and recooled to 0 °C, and then phenyl isocyanate (1.31 g, 0.0110 mol, 1.20 mL) was added rapidly dropwise over 1 min. After 30 min at 0 °C, the mixture was stirred at ambient temperature for 2−12 h (TLC monitoring; THF/H_2O/EtOAc, 10/1/39 or EtOAc/hexane mixtures). The solution was poured into 500-600 mL of ice/water and acidified to pH ∼1−2 with 12 N HCl. After stirring at 0 °C for 30 min, the resultant solid was collected by suction filtration, washed with several portions of ice/water, dried, and recrystallized from the appropriate solvents indicated below to afford **6b,d,e,h−j** as nearly colorless, voluminous solids. Principal IR bands (KBr): 3275, 1715−1720, 1670, 1645, 1590, 1250 cm^{-1}.

***N*-Phenyl 2-[4-(ethoxycarbonyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6b)**: mp 220.5−222.5 °C from THF or acetone; yield 66%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.35 (t, J = 7 Hz, 3H), 4.37 (q, J = 7 Hz, 2H), 5.43 (s, 1H), 6.95−8.15 (m, 13H), 10.8 (br s, 1H); MS (EI) 428 au. Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.09; H, 4.71; N, 6.54. Found: C, 70.42; H, 4.80; N, 6.64.

***N*-Phenyl 2-(3,5-dichlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6d)**: mp 252−254 °C from acetone; yield 69%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 5.37 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.38 (m, 4H), 7.62 (m, 4H), 7.80 (m, 2H), 8.16 (d, J = 8.0 Hz, 1H), 10.8 (br s, 1H); MS (EI) 424, 426 au. Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_3$: C, 62.14; H, 3.32; N, 6.59. Found: C, 62.48; H, 3.28; N, 6.55.

***N*-Phenyl 2-(3,5-dimethoxyphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6e)**: mp 211−213 °C from acetone; yield 86%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.75 (s, 6H), 5.35 (s, 1H), 6.43 (br, 2H), 6.63 (m, 1H), 7.15 (m, 1H), 7.35 (m, 2H), 7.61 (m, 4H), 7.75 (m, 1H), 8.15 (m, 1H), 10.9 (s, 1H); MS (EI) 416 au. Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.51; H, 5.02; N, 6.65.

***N*-Phenyl 2-(3-methyl-4-isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6h)**: mp 200−202 °C from ethyl acetate/hexanes; yield 81%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.25 (d, J = 7.0 Hz, 6H), 2.35 (s, 3H), 3.15 (m, 1H), 5.30 (s, 1H), 6.90−7.22 (m, 3H), 7.35 (m, 4H), 7.41 (m, 4H), 7.75 (m, 1H), 8.12 (m, 1H), 10.7 (s, 1H); MS (EI) 412 au. Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86 N, 6.79. Found: C, 75.53; H, 5.79; N, 6.86.

***N*-Phenyl 2-(4-isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6i)**: mp 217−219 °C from acetone or acetone/hexanes; yield 55%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.30 (d, J = 7.0 Hz, 6H), 3.00 (m, 1H), 5.35 (s, 1H), 7.15 (m, 3H), 7.42 (m, 3H), 7.63 (m, 5H), 7.75 (m, 1H), 8.10 (m, 1H), 11.0 (s, 1H); MS (EI) 398 au. Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.46; H, 5.69; N, 7.09.

***N*-Phenyl 2-[3,5-bis(trifluoromethyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxamide (6j)**: mp 188−190 °C (dec) from acetone or acetone/hexanes; yield 95%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 5.40 (s, 1H), 7.15 (t, J = 7.0 Hz, 1H), 7.40 (t, J = 7.0 Hz, 2H), 7.65 (m, 4H), 7.70 (t, J = 7.0 Hz, 1H), 8.10 (br s, 2H), 8.22 (d, J = 7.0 Hz, 1H), 8.3 (br s, 1H), 11.0 (s, 1H); MS (EI) 492 au. Anal. Calcd for $C_{24}H_{14}F_6N_2O_3$: C, 58.55; H, 2.87; N, 5.69. Found: C, 58.47; H, 2.63; N, 5.47.

Method B-2. General Procedure for the Alcoholysis of the C-4 *N*-Phenylcarboxamide Derivatives 6b,d,e,h−j To Afford Ethyl 2-Aryl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates 3b,d,e,h−j. A suspension of **6b,d,e,h−j** (0.020 mol) in 300−400 mL of ethanol was stirred and heated at reflux for 12−36 h, reaction progress being monitored by TLC (EtOAc/hexane mixtures) as well as by complete dissolution of the starting material. The solution was cooled to ambient temperature and then refrigerated overnight at 0−4 °C. The resultant products were collected by suction filtration and dried to afford nearly colorless crystalline products **3b,d,e,h−j** which were usually obtained in analytically pure form. Where appropriate, recrystallization from ethanol afforded **3b,d,e,h−j** as colorless solids.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3b): mp 176−177 °C; yield 87%; same physical properties and spectra as material prepared above via the ethyl chloroformate protocol.

Ethyl 2-(3,5-Dichlorophenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3d): mp 192−194 °C; yield 87%; same physical properties and spectra as material prepared above via the ethyl chloroformate protocol.

Ethyl 2-(3,5-dimethoxyphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3e): mp 176−177 °C; yield 88%; same physical properties and spectra as material prepared above via the ethyl chloroformate protocol.

Ethyl 2-(3-methyl-4-isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3h): mp 135−137 °C; yield 79%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 7.0 Hz, 6H), 1.55 (t, J = 7.0 Hz, 3H), 2.40 (s, 3H), 3.21 (m, 1H), 4.25 + 4.55 (2 q, J = 7.0 Hz, 2H), 7.00−7.73 (m, 5H), 8.41 (dd, J = 7.2, 2.1 Hz, 1H), 8.55 (d, J = 7.2 Hz, 1H); MS (EI) 365 au. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.65; H, 6.63; N, 3.76.

Ethyl 2-(4-isopropylphenyl)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3i): mp 160−161.5 °C; yield 81%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 8.0 Hz, 6H), 1.55 (t, J = 7.4 Hz, 3H), 3.00 (m, 1H), 4.60 (q, J = 7.4 Hz, 2H), 7.12−7.62 (m, 5H), 7.70 (m, 1H), 8.40 (dd, J = 7.2, 2.1 Hz, 1H), 8.55 (dd, J = 7.2, 2.1 Hz, 1H); MS (EI) 351 au. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.59; H, 5.83; N, 3.94.

Ethyl 2-[3,5-bis(trifluoromethyl)phenyl]-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (3j): mp 161−163 °C; yield 62%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 + 1.60 (2t, J = 7.2 Hz, 3H), 4.32 + 4.60 (2q, J = 7.2 Hz, 2H), 7.31−8.10 (m, 5H), 8.40 (m, 1H), 8.55 (d, J = 7.2 Hz, 1H); MS (EI) 445 au. Anal. Calcd for $C_{20}H_{13}F_6NO_4$: C, 53.94; H, 2.94; N, 3.15. Found: C, 54.17; H, 3.08; N, 3.37.

General Procedure for the Benzoyloxyation of 3a−j. Synthesis of Ethyl 2-Aryl-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylates 4a−j. To a magnetically stirred suspension of sodium hydride (0.26 g, 0.011 mol, from 0.43 g of 60% oil dispersion, washed three times with dry hexane) in 50 mL of anhydrous THF at 0 °C was added intermediate 3a−j (0.010 mol) portionwise over 10−15 min. After stirring at 0 °C for 1 h, a solution of benzoyl peroxide (2.67 g, 0.011 mol) in 25 mL of anhydrous THF was added dropwise over 15 min. The

ice bath was removed, and the mixture was stirred at ambient temperature for 6−24 h, reaction progress being monitored by TLC (EtOAc/hexane or methylene chloride/ethyl acetate mixtures). The solvent was evaporated, and the residue was dissolved in 300 mL of methylene chloride and extracted with 2 × 50 mL portions each of saturated sodium bicarbonate solution and water. Drying over anhydrous $MgSO_4$, filtration, and solvent removal afforded the crude product, which was purified either by recrystallization from ethanol/acetone or ethyl acetate/hexane mixtures or by flash chromatography using ethyl acetate/hexane or ethyl acetate/methylene chloride gradient systems to afford the products **4a**−**j** as nearly colorless solids. Range of principal IR bands for **4a**−**j** in KBr: 1755−1765, 1715−1720, 1670−1680, 1585−1590 $cm.^{-1}$

Ethyl 2-phenyl-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4a): mp 232−234 °C; yield 89%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.23 (t, J = 7 Hz, 3H), 4.25 (dq, each J = 7 Hz, 2H), 7.12−8.43 (m, 14H); MS (EI) 429 au. Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92; H, 4.46; N, 3.26. Found: C, 69.73; H, 4.50; N, 3.34.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]-4-(benzoyloxy)-1,3-(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4b): glass; yield 92%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.25 (t, J = 7 Hz, 3H), 1.38 (t, J = 7 Hz, 3H), 4.38 (dq, each J = 7 Hz, 4H), 7.20−8.45 (m, 13H); MS (EI) 501 au. Anal. Calcd for $C_{28}H_{23}NO_8$: C, 67.06; H, 4.62; N, 2.79. Found: C, 67.40; H, 4.95; N, 3.12.

Ethyl 2-(4-chlorophenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4c): mp 232−235 °C; yield 92%; ^{1}H-NMR (60 MHz, DMSO-d_6) δ 1.23 (t, J = 7 Hz, 3H), 4.27 (dq, each J = 7 Hz, 2 H), 7.05−8.45 (m, 13H); MS (EI) 462, 464 au. Anal. Calcd for $C_{25}H_{18}ClNO_6$: C, 64.73; H, 3.91; N, 3.02. Found: C, 65.01; H, 3.94; N, 3.14.

Ethyl 2-(3,5-dichlorophenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4d): mp 181−183 °C; yield 89%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H), 4.30 (m/overlapping q, 2H), 7.25 (m, 2H), 7.50 (m, 3H), 7.66 (m, 4H), 8.18 (m, 2H), 8.33 (d, J = 8.0 Hz, 1H); MS (EI) 497, 499 au. Anal. Calcd for $C_{25}H_{17}Cl_2NO_6$: C, 60.26; H, 3.44; N, 2.81. Found: C, 59.89; H, 3.41; N, 2.75.

Ethyl 2-(3,5-dimethoxyphenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4e): mp 166−167 °C; yield 75%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 3.80 (s, 6H), 4.20 (m, 1H), 4.35 (m, 1H), 6.45 (d, J = 2.1 Hz, 2H), 7.40−7.73 (m, 6H), 8.21 (m, 2H), 8.35 (m, 1H); MS (EI) 489 au. Anal. Calcd for $C_{27}H_{23}NO_8$: C, 66.25; H, 4.74; N, 2.86. Found: C, 66.31; H, 4.95; N, 3.04.

Ethyl 2-(4-methylphenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4f): mp 243−245 °C; yield 72%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 2.40 (s, 3H), 4.11−4.43 (overlapping q, J = 7.0 Hz, 2H), 7.23−7.70 (m, 10H), 8.10−8.43 (m, 3H); MS (EI) 443 au. Anal. Calcd for $C_{26}H_{21}NO_6$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.26; H, 4.68; N, 3.27.

Ethyl 2-(3-methylphenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4g): mp 214−217 °C; yield 50%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3H), 2.42 (s, 3H), 4.13−4.40 (2 overlapping q, J = 7.5 Hz, 2H), 7.10−7.83 (m, 10H), 8.10−8.44 (m, 3H); MS (EI) 443 au. Anal. Calcd for $C_{26}H_{21}NO_6$: C, 70.42; H, 4.77; N, 3.16. Found: C, 70.53; H, 4.91; N, 3.34.

Ethyl 2-(3-methyl-4-isopropylphenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4h): mp 149−151 °C; yield 85%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 9H), 2.20 (s, 3H), 3.11 (m, 1H), 4.25 (2 overlapping q, J = 7.0 Hz, 2H), 7.12 (m, 2H), 7.32−7.71 (m, 7H), 8.15 (m, 2H), 8.21 (m, 1H); MS(EI) 485 au. Anal. Calcd for $C_{29}H_{27}NO_6$: C, 71.74; H, 5.61; N, 2.88. Found: C, 71.97; H, 5.87; N, 3.14.

Ethyl 2-(4-isopropylphenyl)-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4i): mp 165−167 °C; yield 78%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 9H), 3.02 (m, 1H), 4.20 (q, J = 7.2 Hz, 1H), 4.35 (q, J = 7.2 Hz, 1H), 7.23−7.72 (m, 10H), 8.21 (dd, J = 8.2, 2.1 Hz, 2H), 8.35 (d, J = 7.0 Hz, 1H); MS(EI) 471 au. Anal. Calcd for $C_{28}H_{25}NO_6$: C, 71.33; H, 5.34; N, 2.97. Found: C, 71.47; H, 5.39; N, 3.04.

Ethyl 2-[3,5-bis(trifluoromethyl)phenyl]-4-(benzoyloxy)-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (4j): mp 164−166 °C; yield 63%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 4.25 (m, 1H), 4.40 (m, 1H), 7.50 (t, J = 8.2 Hz, 2H), 7.65 (m, 4H), 7.81 (s, 2H), 8.00 (s, 1H), 8.23 (dd, J = 7.2, 2.1 Hz, 2H), 8.35 (d, J = 7.2 Hz, 1H); MS (EI) 565 au. Anal. Calcd for $C_{27}H_{17}F_6NO_6$: C, 57.35; H, 3.03; N, 2.48. Found: C, 57.18; H, 2.97; N, 2.76.

General Procedure for the Cleavage of the C-4 Benzoyloxy Intermediates 4a−j. Synthesis of Ethyl 2-Aryl-4-hydroxy-1,3(2*H*,4*H*)-Dioxoisoquinoline-4-carboxylates 5a−j. To a magnetically stirred solution of intermediate **4a**−**j** (7.5 mmol) in 50 mL of anhydrous ethanol at 0 °C was added slowly over 20 min a solution of sodium ethoxide freshly prepared from sodium (0.045−0.075 mol) and 15−25 mL of anhydrous ethanol. The mixture was stirred at 0 °C for 15−60 min; progress of the reaction was monitored by TLC analysis (EtOAc/hexane or methylene chloride/ethyl acetate mixtures). Upon completion, the reaction was neutralized at 0 °C with the theoretical amount of acetic acid (0.045−0.075 mol). The solvent was evaporated, and the residue was dissolved in 300 mL of ethyl acetate, mixed with $MgSO_4$ (to assist with the filtration of colloidal NaOAc), filtered, and evaporated. The crude product was purified by flash chromatography, employing methylene chloride/hexane to methylene chloride/ethyl acetate gradient systems to afford the pure products **5a**−**j**. Analytical samples, usually appearing as colorless needles, were obtained by recrystallization from ether/hexane mixtures. Range of principal IR bands for **5a**−**j** in KBr: 3200−3320, 1745−1755, 1685−1690, 1660−1665, 1595−1605 $cm.^{-1}$

Ethyl 2-phenyl-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5a): mp 97.5−98.5 °C; yield 54%; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.00 (t, J = 7 Hz, 3H), 4.03 (dq, each J = 7 Hz, 2H), 5.10 (br s, 1H), 7.20−8.05 (m, 9H); MS (EI) 325 au. Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.85; H, 5.03; N, 4.58.

Ethyl 2-[4-(Ethoxycarbonyl)phenyl]-4-hydroxy-1,3-(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5b): mp 110−111 °C; yield 45%; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.98 (t, J = 7 Hz, 3H), 1.37 (t, J = 7 Hz, 3H), 4.07 (dq, each J = 7 Hz, 2H), 4.37 (q, J = 7 Hz, 2H), 5.20 (s, 1H), 7.40−8.25 (m, 8H); MS (EI) 397 au. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.75; H, 5.00; N, 3.50.

Ethyl 2-(4-chlorophenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5c): mp 113.5−115 °C; yield 51%; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.02 (t, J = 7 Hz, 3H), 4.08 (dq, each J = 7 Hz, 2 H), 5.12 (s, 1H), 7.13−8.05 (m, 8H); MS(EI) 358, 360 au. Anal. Calcd for $C_{18}H_{14}ClNO_5$: C, 60.09; H, 3.92; N, 3.89. Found: C, 60.33; H, 4.21; N, 4.20.

Ethyl 2-(3,5-dichlorophenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5d): mp 148−150 °C; yield 52%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 7.0 Hz, 3H), 4.17 (m, 2H), 4.95 (s, 1H), 7.32 (m, 1H), 7.47−7.70 (m, 5H), 7.92 (d, J = 8.2 Hz, 1H); MS(EI) no molecular ion. Anal. Calcd for $C_{18}H_{13}Cl_2NO_5$: C, 54.84; H, 3.32; N, 3.55. Found: C, 54.96; H, 3.64; N, 3.80.

Ethyl 2-(3,5-dimethoxyphenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5e): mp 124−125 °C; yield 47%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.0 Hz, 3H), 3.82 (s, 6H), 4.10−4.43 (2 overlapping q, J = 7.0 Hz, 2H), 4.91 (s, 1H), 6.45 (m, 1H), 6.70 (m, 2H), 7.53 (m, 1H), 7.65 (m, 2H), 7.93 (m, 1H); MS(EI) 385 au. Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.57; H, 5.15; N, 3.87.

Ethyl 2-(4-methylphenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5f): mp 118−120 °C; yield 49%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J = 6.5 Hz, 3H), 2.41 (s, 3H), 4.00−4.32 (m, 2H), 4.85 (s, 1H), 7.20−8.02 (m, 8H); MS-(EI) 339 au. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.08; H, 5.00; N, 4.25.

Ethyl 2-(3-methylphenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5g): mp 144−145 °C; yield 46%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7.0 Hz, 3H), 2.44 (s, 3H), 4.03−4.38 (m, 2H), 5.00 (s, 1H), 7.15−7.92 (m, 8H); MS-(EI) 339 au. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.19; H, 5.07; N, 4.36.

Ethyl 2-(3-methyl-4-isopropylphenyl)-4-hydroxy-1,3-(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5h): mp 164−166 °C; yield 61%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (t, J = 7.1 Hz, 3H), 1.25 (d, J = 8.0 Hz, 6H), 2.30 (s, 3H), 3.14 (m, 1H), 4.24 (2 overlapping q, J = 7.1 Hz, 2H), 4.83 (br s, 1H), 7.15−7.35 (m, 3H), 7.42−7.70 (m, 3H), 7.92 (dd, J = 8.1, 2.1 Hz, 1H); MS(EI)

381 au. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.47; H, 6.26 ; N, 3.90.

Ethyl 2-(4-isopropylphenyl)-4-hydroxy-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5i): mp 133−134 °C; yield 38%; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.00 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 8.1 Hz, 6H), 2.92 (m, 1H), 3.97 (q, J = 7.2 Hz, 1H), 4.13 (q, J = 7.2 Hz, 1H), 7.20−7.81 (m, 8H); MS(EI) 367 au. Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.97; H, 5.95; N, 4.04.

Ethyl 2-[3,5-bis(trifluoromethyl)phenyl]-4-hydroxy-1,3-(2*H*,4*H*)-dioxoisoquinoline-4-carboxylate (5j): mp 123−125 °C; yield 49%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 7.1 Hz, 3H), 4.05 (m, 1H), 4.25 (m, 1H), 5.02 (s, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.62−7.81 (m, 3H), 7.85 (s, 1H), 7.95 (d, J = 7.0 Hz, 1H), 8.10 (s, 2H); MS(EI) 461 au. Anal. Calcd for $C_{20}H_{13}F_6NO_5$: C, 52.07; H, 2.84; N, 3.04. Found: C, 52.39; H, 3.17; N, 3.33.

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