HETEROCYCLES, Vol. 62, 2004, pp. 491 - 501
Received, 31st July, 2003, Accepted, 5th September, 2003, Published online, 27th October, 2003

REGIOSELECTIVE AROMATIC SUBSTITUTION OF 6,8-DIHYDROXY-4-ETHOXYCARBONYL-2*H*-ISOQUINOLIN-1-ONE DERIVATIVES USING THE STILLE COUPLING REACTION

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Abstract – The novel synthesis of 6- or 7-aromatic substituted 2*H*-isoquinolin-1-ones, by two different routes is described. In the first route, 7-substituted derivatives were prepared by regioselective iodination at the 7-position of 6,8-dihydroxy-4-ethoxycarbonyl-2*H*-isoquinolin-1-one derivatives **(1)** followed by the Stille coupling reaction. In the second route, 6-subsutituted derivatives were prepared by the selective triflation of the 6-hydroxy group of **1** followed by the Stille coupling reaction.

Isoquinolin-1-ones represent an interesting structural class of compounds, which have been found many uses in the fields of medicinal and synthetic chemistry. We have previously described the ring-transformation[1] of 6-methyl-4*H*-1,3-oxazin-4-ones with diethyl 1,3-acetonedicarboxylate to yield the 6,8-dihydroxy-4-ethoxycarbonyl-2*H*-isoquinolin-1-one derivatives **(1)**.[2] 2*H*-Isoquinolin-1-one derivatives **(1)** have been shown to exhibit anticancer activity,[3] and are valuable intermediates in the synthesis of potentially antitumor indenoquinoline derivatives.[4] Our attention has recently been focused on the further functionalization of 2*H*-isoquinolin-1-one derivatives **(1)**. In this paper we describe a novel synthesis of 6- or 7-aromatic substituted 2*H*-isoquinolin-1-one using the Stille coupling reaction[5] *via* the regioselective iodination and triflation of 2*H*-isoquinolin-1-one derivatives **(1)**.

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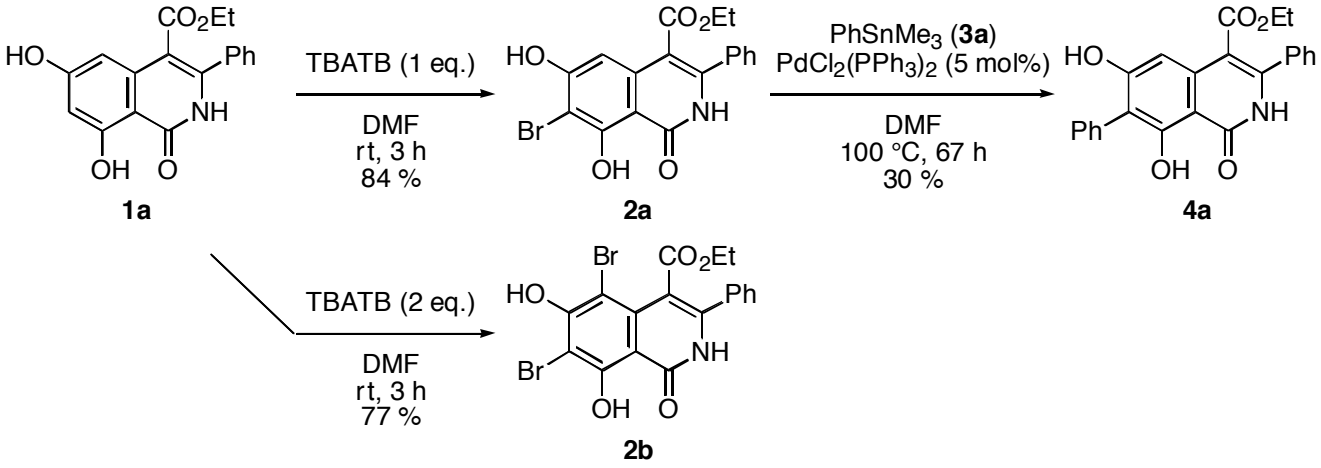
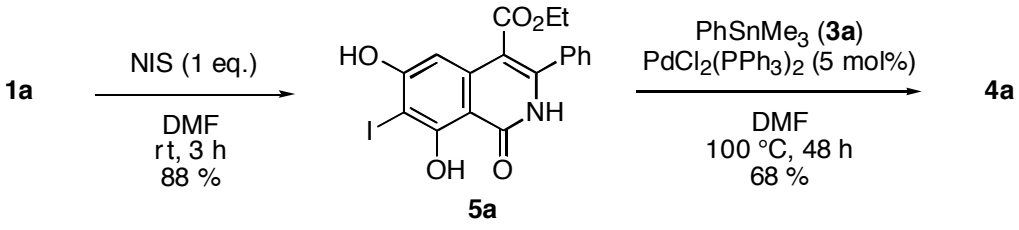
†This paper is dedicated to Professor Leo A. Paquette on his 70 th birthday.

The bromination of 2*H*-isoquinolin-1-one (**1a**) was initially examined. The regioselective monobromination of **1a** took place at the 7-position; the reaction of **1a** with 1 equivalent of tetrabutylammonium tribromide (TBATB)[6] at room temperature gave 7-bromo-2*H*-isoquinolin-1-one (**2a**) in 84% yield. The use of 2 equivalents of TBATB in this reaction resulted in dibromination, giving the 5,7-dibromo-6,8-dihydro-4-ethoxycarbonyl-3-phenyl-2*H*-isoquinolin-1-one (**2b**) in 77% yield. In contrast, employing 1 equivalent of bromine (Br_2) or *N*-bromosuccinimide (NBS) instead of TBATB afforded a small amount of the 5,7-dibromo derivative (**2b**) along with starting material. The Stille coupling reaction of **2a** was performed with trimethyl(phenyl)stannane (**3a**) using bis(triphenylphosphine)palladium(II) dichloride (5 mol%) as a catalyst in DMF at 100 °C for 67 h. The yield of 7-phenyl derivative (**4a**) was 30%. The use of tetrakis(triphenylphosphine)palladium(0) or palladium(II) acetate as catalyst, resulted in no reaction and the recovery of the starting materials.



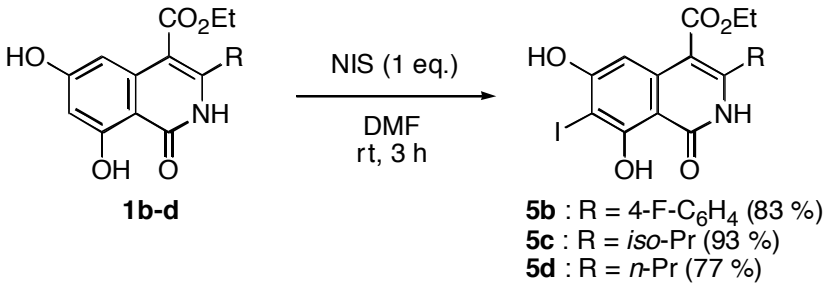
Scheme 1

In the palladium-catalyzed coupling of aryl halides, the usual order of reactivity is I > Br >> Cl.[7] Accordingly, the bromide (**2a**) was replaced with the iodide (**5a**) in order to improve product yield. The regioselective monoiodination of **1a** was carried out as follows: the treatment of **1a** with 1 equivalent of *N*-iodosuccinimide (NIS) in DMF at room temperature for 3 h, to give **5a** in 88% yield. The Stille coupling reaction of **5a** with **3a** gave **4a** in 68% yield.



Scheme 2

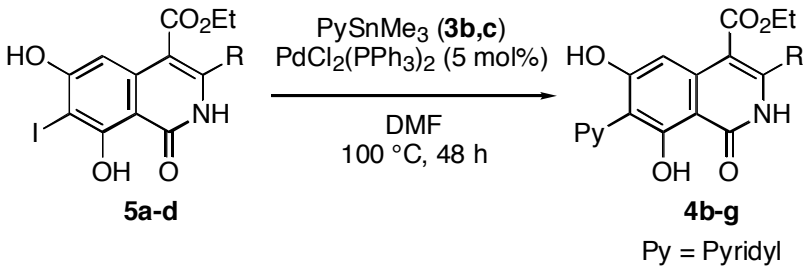
Given the above encouraging results, the coupling reactions of other 2*H*-isoquinolin-1-ones (**1b–d**) *via* 7-iodo-2*H*-isoquinolin-1-ones (**5b–d**) were examined. The reaction between 2*H*-isoquinolin-1-one (**1b–d**) and NIS gave the corresponding 7-iodo-*2H*-isoquinolin-1-one derivatives (**5b–d**) in 77–93% yields, respectively (Scheme 3).



Scheme 3

The Stille coupling reactions of **5a–d** with 3-trimethylstannylpyridine (**3b**) and 2-trimethylstannylpyridine (**3c**) were also carried out and the results are summarized in Table 1.

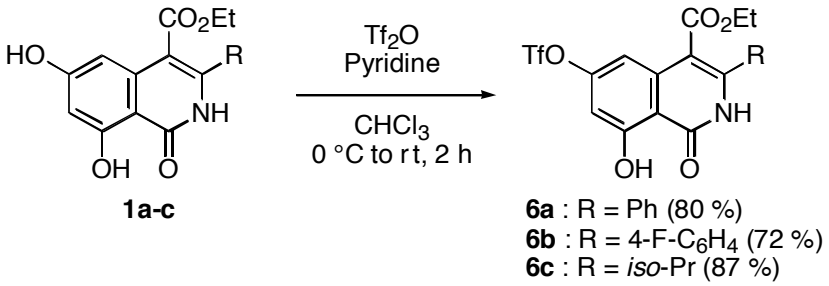
Table 1. Stille Coupling Reactions of **5a-d** with **3b,c**



Entry	R	Py	Product	Yield (%)
1	Ph	3-Pyridyl	**4b**	66
2	4-F-C_6H_4	3-Pyridyl	**4c**	60
3	*iso*-Pr	3-Pyridyl	**4d**	68
4	*iso*-Pr	2-Pyridyl	**4e**	56
5	*n*-Pr	3-Pyridyl	**4f**	47
6	*n*-Pr	2-Pyridyl	**4g**	42

We next turned our attention to the conversion of the hydroxy group to a triflate. Treatment of **1a** with trifluorosulfonic anhydride (Tf_2O) in the presence of pyridine resulted in the regioselective triflation at the 6-position to give 6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one (**6a**) in 87% yield. In a similar manner, 6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one derivatives (**6b,c**) were also obtained

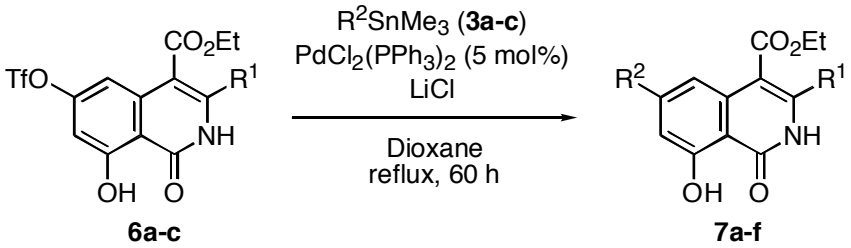
(Scheme 4). The difference in the reactivity of the two hydroxyl groups at the 6- and 8-positions can be rationalized as follows: the hydroxyl group at the 8-position of **1** would presumably form an intramolecular hydrogen bond with the carbonyl group at the 1-position.



Scheme 4

In addition, the Stille coupling reaction of **6a** with **3a** proceeded smoothly to give 6-phenyl-2*H*-isoquinolin-1-one (**7a**) in 68% yield. Analogously, the reaction of **6a-c** with **3a-c** afforded the corresponding **7b-f** in 63-72% yields. These results obtained are summarized in Table 2.

Table 2. Stille Coupling Reactions of **6a-c** with **3a-c**



Entry	R^1	R^2	Product	Yield (%)
1	Ph	Ph	**7a**	68
2	Ph	3-Pyridyl	**7b**	70
3	4-F-C_6H_4	3-Pyridyl	**7c**	60
4	*iso*-Pr	Ph	**7d**	70
5	*iso*-Pr	2-Pyridyl	**7e**	63
6	*iso*-Pr	3-Pyridyl	**7f**	72

In summary, we demonstrate here, the synthesis of novel poly-functionalized 2*H*-isoquinolin-1-ones (**4**) and (**7**) *via* the regioselective iodination and triflation of **1** followed by the Stille coupling reaction of the resulting 2*H*-isoquinolin-1-ones (**5**) and (**6**).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. MS spectra were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX270 or JNM-PMX60si spectrometer, using tetramethylsilane as an internal standard. Column chromatography was carried out on Merck Silica Gel 60 (230-400 mesh for flash chromatography).

7-Bromo-6,8-dihydroxy-4-ethoxycarbonyl-3-phenyl-2*H*-isoquinolin-1-one (2a)

A solution of tetrabutylammonium tribromide (14.5 g, 30 mmol) in dry DMF (20 mL) was added dropwise to a stirred solution of 2*H*-isoquinolin-1-one (**1a**)(9.76 g, 30 mmol) in dry DMF (50 mL), with stirring for 3 h at rt. The reaction mixture was quenched by slowly adding a water. The precipitated crystalline product was separated from the solution by filtration, washed with 10% HCl, and recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 10.2 g (84%) of **2a**, mp 263-264 °C. IR (KBr) cm^{-1}: 1638, 1630. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) □: 0.86 (3H, t, *J* = 7 Hz), 4.02 (2H, q, *J* = 7 Hz), 6.89 (1H, s), 7.50 (5H, s), 10.83 (1H, s), 11.75 (1H, br s), 12.95 (1H, s). MS (*m/z*): 403 (M^+-1), 405 (M^++1). *Anal.* Calcd $C_{18}H_{14}NO_5Br$: C, 53.49; H, 3.49; N, 3.47. Found: C, 53.23; H, 3.58; N, 3.55.

5,7-Dibromo-6,8-dihydroxy-4-ethoxycarbonyl-3-phenyl-2*H*-isoquinolin-1-one (2b)

A solution of tetrabutylammonium tribromide (2.9 g, 6 mmol) in dry DMF (10 mL) was added dropwise to a stirred solution of 2*H*-isoquinolin-1-one (**1a**)(1.0 g, 3 mmol) in dry DMF (10 mL), with stirring for 3 h at rt. The reaction mixture was quenched by slowly adding a water. The precipitated crystalline product was separated from the solution by filtration, washed with 10% HCl, and recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 1.12 g (77%) of **2b**, mp 263-264 °C (decomp). IR (KBr) cm^{-1}: 1701, 1654. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) □: 1.00 (3H, t, *J* = 7 Hz), 3.98 (2H, q, *J* = 7 Hz), 7.48 (5H, s), 10.09 (1H, br s), 11.97 (1H, br s), 14.70 (1H, s). MS (*m/z*): 482 (M^+-1). *Anal.* Calcd $C_{18}H_{13}NO_5Br_2$: C, 44.75; H, 2.71; N, 2.90. Found: C, 45.01; H, 2.98; N, 3.11.

General Procedure for the Synthesis of 5a–d

A solution of *N*-iodosuccinimide (6.72 g, 30 mmol) in dry DMF (20 mL) was added dropwise to a stirred solution of isoquinolin-1-one derivative (**1a-d**)(30 mmol) in dry DMF (50 mL), with stirring for 3 h at rt. The reaction mixture was quenched by slowly adding a water. The precipitated crystalline product was separated from the solution by filtration, washed with 10% HCl, and purified by recrystallization.

6,8-Dihydroxy-4-ethoxycarbonyl-7-iodo-3-phenyl-2*H*-isoquinolin-1-one (5a)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 11.9 g (88%) of **5a**, mp 264-265 °C (decomp). IR (KBr) cm^{-1}: 1682, 1651. ^{1}H-NMR (270 MHz, DMSO-d_6) □: 0.82 (3H, t, *J* = 7.1 Hz), 3.96 (2H, q, *J* = 7.1 Hz), 6.77 (1H, s), 7.44-7.52 (5H, m), 11.36 (1H, s), 12.12 (1H, s), 14.22 (1H, s). MS (*m*/*z*): 451 (M^+). *Anal.* Calcd $C_{18}H_{14}NO_5I$: C, 47.91; H, 3.13; N, 3.10. Found: C, 47.66; H, 2.89; N, 2.97.

6,8-Dihydroxy-4-ethoxycarbonyl-3-(4-fluorophenyl)-7-iodo -2*H*-isoquinolin-1-one (5b)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 11.7 g (83%) of **5b**, mp 239-240 °C (decomp). IR (KBr) cm^{-1}: 1670, 1630. ^{1}H-NMR (270 MHz, DMSO-d_6) □: 0.89 (3H, t, *J* = 7.1 Hz), 3.99 (2H, q, *J* = 7.1 Hz), 6.82 (1H, s), 7.27-7.34 (2H, m), 7.45-7.53 (2H, m), 11.26 (1H, s), 12.14 (1H, s), 14.01 (1H, s). MS (*m*/*z*): 469 (M^+). *Anal.* Calcd $C_{18}H_{13}NO_5FI$: C, 46.08; H, 2.79; N, 2.99. Found: C, 46.33; H, 2.86; N, 3.19.

6,8-Dihydroxy-4-ethoxycarbonyl-7-iodo-3-isopropyl-2*H*-isoquinolin-1-one (5c)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 11.64 g (93%) of **5c**, mp 243-254 °C (decomp). IR (KBr) cm^{-1}: 1693, 1652. ^{1}H-NMR (270 MHz, DMSO-d_6) □: 1.27 (6H, d, *J* = 6.9 Hz), 1.34 (3H, *J* = 7.1 Hz), 2.93-3.03 (1H, m), 4.35 (2H, q, *J* = 7.1 Hz), 6.52 (1H, s), 11.28 (1H, s), 11.61 (1H, s), 14.17 (1H, s). MS (*m*/*z*): 417 (M^+). *Anal.* Calcd $C_{15}H_{16}NO_5I$: C, 43.18; H, 3.87; N, 3.36. Found: C, 43.23; H, 3.96; N, 3.38.

6,8-Dihydroxy-4-ethoxycarbonyl-7-iodo-3-*n*-propyl-2*H*-isoquinolin-1-one (5d)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 9.64 g (77%) of **5d**, mp 257-259 °C (decomp). IR (KBr) cm^{-1}: 1694, 1652. ^{1}H-NMR (270 MHz, DMSO-d_6) □: 0.89 (3H, t, *J* = 7.4 Hz), 1.34 (3H, t, *J* = 7.1 Hz), 1.58-1.67 (2H, m), 2.52 (2H, t, *J* = 7.4 Hz), 4.34 (2H, q, *J* = 7.1 Hz), 6.67 (1H, s), 11.26 (1H, s), 11.87 (1H, s), 14.12 (1H, s). MS (*m*/*z*): 417 (M^+). *Anal.* Calcd $C_{15}H_{16}NO_5I$: C, 43.18; H, 3.87; N, 3.36. Found: C, 43.06; H, 3.88; N, 3.45.

General Procedure for the Synthesis of 4a–f

Under Ar atmosphere, a mixture of 7-iodo-*2H*-isoquinolin-1-one derivative (**5a-d**)(2 mmol), trimethylstannyl derivative (**3a-c**)(4 mmol), and $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) in dry DMF (20 mL) was heated at 100 °C for 48 h. The reaction mixture was quenched by slowly adding a water. The precipitated crystalline product was separated from the solution by filtration, washed with 10% HCl, and purified by recrystallization.

6,8-Dihydroxy-3,7-diphenyl-4-ethoxycarbonyl-2*H*-isoquinolin-1-one (4a)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 546 mg (68%) of **4a**, mp 258-260 °C (decomp). IR (KBr) cm^{-1}: 1686, 1629. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 0.88 (3H, t, *J* = 7 Hz), 4.03 (2H, q, *J* = 7 Hz), 6.98 (1H, s), 7.45-7.60 (10H, m), 9.63 (1H, br s), 11.12 (1H, br s), 13.33 (1H, s). MS (*m*/*z*): 401 (M^+). *Anal.* Calcd $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49. Found: C, 72.02; H, 4.76; N, 3.47.

6,8-Dihydroxy-4-ethoxycarbonyl-3-phenyl-7-(3-pyridyl)-2*H*-isoquinolin-1-one (4b)

Recrystallized from acetone. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 531 mg (66%) of **4b**, mp 273-275 °C (decomp). IR (KBr) cm^{-1}: 1715, 1634. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7 Hz), 4.03 (2H, q, *J* = 7 Hz), 6.97 (1H, s), 7.47 (5H, s), 7.47-8.87 (4H, m), 10.07 (1H, s), 11.12 (1H, br s), 13.15 (1H, s). MS (*m*/*z*): 402 (M^+). *Anal.* Calcd $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.56; H, 4.62; N, 7.11.

6,8-Dihydroxy-4-ethoxycarbonyl-3-(4-fluorophenyl)-7-(3-pyridyl)-2*H*-isoquinolin-1-one (4c)

Recrystallized from acetone. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 505 mg (60%) of **4c**, mp 274-275 °C (decomp). IR (KBr) cm^{-1}: 1715, 1655. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 0.91 (3H, t, *J* = 7.1 Hz), 4.01 (2H, q, *J* = 7.1 Hz), 6.81 (1H, s), 7.30-7.37 (2H, m), 7.43 (1H, dd, *J* = 7.7, 4.8 Hz), 7.49-7.55 (2H, m), 7.79-7.83 (1H, m), 8.47 (1H, d, *J* = 3.6 Hz), 8.59 (1H, s), 10.69 (1H, s), 12.03 (1H, s), 13.64 (1H, s). MS (*m*/*z*): 420 (M^+). *Anal.* Calcd $C_{23}H_{17}N_2O_5F$: C, 65.71; H, 4.08; N, 6.66. Found: C, 65.82; H, 4.16; N, 6.86.

6,8-Dihydroxy-4-ethoxycarbonyl-3-isopropyl-7-(3-pyridyl)-2*H*-isoquinolin-1-one (4d)

Recrystallized from acetone. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 501 mg (68%) of **4d**, mp 278-280 °C (decomp). IR (KBr) cm^{-1}: 1725, 1631. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 1.28 (6H, d, *J* = 7.1 Hz), 1.35 (3H, t, *J* = 7.1 Hz), 2.94-3.04 (1H, m), 4.36 (2H, q, *J* = 7.1 Hz), 6.55 (1H, s), 7.42 (1H, dd, *J* = 7.8, 4.8 Hz), 7.77-7.80 (1H, m), 8.47 (1H, dd, *J* = 4.8, 1.5 Hz), 8.56 (1H, d, *J* = 1.5 Hz), 10.63 (1H, br s), 11.52 (1H, br s), 13.62 (1H, s). MS (*m*/*z*): 368 (M^+). *Anal.* Calcd $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.32; H, 5.38; N, 7.89.

6,8-Dihydroxy-4-ethoxycarbonyl-3-isopropyl-7-(2-pyridyl)-2*H*-isoquinolin-1-one (4e)

Recrystallized from acetone. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 412 mg (56%) of **4e**, mp 291-293 °C (decomp). IR (KBr) cm^{-1}: 1728, 1634. ^{1}H-NMR (60 MHz, $CDCl_3$ +

DMSO-d_6) δ: 1.32-1.55 (9H, m), 2.17-2.62 (1H, m), 4.47 (2H, q, *J* = 7 Hz), 6.50 (1H, s), 7.33-8.97 (4H, m), 10.32 (1H, s), 11.03 (1H, s), 15.17 (1H, s). MS (*m*/*z*): 368 (M^+). *Anal.* Calcd $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.41; H, 5.69; N, 7.88.

6,8-Dihydroxy-4-ethoxycarbonyl-3-*n*-propyl-7-(3-pyridyl)-2*H*-isoquinolin-1-one (4f)

Recrystallized from acetone. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 346 mg (47%) of **4f**, mp 254-256 °C (decomp). IR (KBr) cm^{-1}: 1705, 1643. ^{1}H-NMR (270 MHz, DMSO-d_6) δ: 0.91 (3H, t, *J* = 7.3 Hz), 1.35 (3H, t, *J* = 7.1 Hz), 1.60-1.69 (2H, m), 2.56 (2H, t, *J* = 7.3 Hz), 4.36 (2H, q, *J* = 7.1 Hz), 6.71 (1H, s), 7.40-7.45 (1H, m), 7.78 (1H, d, *J* = 7.9 Hz), 8.38- 8.65 (2H, m), 10.61 (1H, s), 11.78 (1H, s), 13.59 (1H, s). MS (*m*/*z*): 368 (M^+). *Anal.* Calcd $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.39; H, 5.46; N, 7.64.

6,8-Dihydroxy-4-ethoxycarbonyl-3-*n*-propyl-7-(2-pyridyl)-2*H*-isoquinolin-1-one (4g)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 309 mg (42%) of **4g**, mp 297-298 °C (decomp). IR (KBr) cm^{-1}: 1724, 1642. ^{1}H-NMR (60 MHz, $CDCl_3$ + DMSO-d_6) δ: 1.03 (3H, t, *J* = 7 Hz), 1.33-1.97 (5H, m), 2.72 (2H, t, *J* = 7 Hz), 4.43 (2H, q, *J* = 7 Hz), 6.67 (1H, s), 7.34-8.98 (4H, m), 11.33 (1H, s), 13.83 (1H, s), 15.10 (1H, s). MS (*m*/*z*): 368 (M^+). *Anal.* Calcd $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.46; H, 5.44; N, 7.64.

General Procedure for the Synthesis of 6a–d

A solution of trifluoromethanesulfonic anhydride (3.10 g, 11 mmol) in dry $CHCl_3$ (20 mL) was added dropwise to a stirred solution of isoquinolin-1-one derivative (**1a-c**)(10 mmol) and dry pyridine (1.6 g, 20 mmol) in dry $CHCl_3$ (50 mL) at 0 °C, with stirring for 2 h at rt. The reaction mixture was quenched by slowly adding a water. The $CHCl_3$ layer was separated from the aqueous layer. Then the $CHCl_3$ layer was washed with 10% HCl and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallization.

4-Ethoxycarbonyl-8-hydroxy-3-phenyl-6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one (6a)

Recrystallized from ether. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 3.66 g (80%) of **6a**, mp 188-190 °C. IR (KBr) cm^{-1}: 1734, 1651. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.1 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 6.83 (1H, d, *J* = 2.3 Hz), 7.33 (1H, d, *J* = 2.3 Hz), 7.49–7.61 (5H, m), 11.06 (1H, br s), 12.27 (1H, s). MS (*m*/*z*): 457 (M^+). *Anal.* Calcd $C_{19}H_{14}NO_7F_3S$: C, 49.89; H, 3.09; N, 3.06. Found: C, 50.10; H, 3.16; N, 2.88.

4-Ethoxycarbonyl-3-(4-fluorophenyl)-8-hydroxy-6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one (6b)

Recrystallized from ether. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 3.42 g (72%) of **6b**, mp 187-188 °C. IR (KBr) cm^{-1}: 1716, 1648. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.00 (3H, t, *J* = 7.1 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 6.86 (1H, d, *J* = 2.3 Hz), 7.20–7.31 (3H, m), 7.47–7.53 (2H, m), 10.15 (1H, br s), 12.35 (1H, s). MS (*m/z*): 475 (M^+). *Anal.* Calcd $C_{19}H_{13}NO_7F_4S$: C, 48.01; H, 2.76; N, 2.95. Found: C, 48.10; H, 3.01; N, 2.86.

4-Ethoxycarbonyl-3-isopropyl-8-hydroxy-6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one (6c)

Recrystallized from ethyl acetate. The combined crystalline product was dried over P_2O_5 *in vacuo* to give 3.68 g (87%) of **6c**, mp 212-214 °C. IR (KBr) cm^{-1}: 1710, 1648. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.37-1.46 (9H, m), 3.28-3.39 (1H, m), 4.46 (2H, q, *J* = 7.1 Hz), 6.80 (1H, d, *J* = 2.2 Hz), 7.15 (1H, d, *J* = 2.3 Hz), 10.14 (1H, br s), 12.654 (1H, s). MS (*m/z*): 423 (M^+). *Anal.* Calcd $C_{16}H_{16}NO_7F_3S$: C, 45.39; H, 3.81; N, 3.31. Found: C, 45.68; H, 3.78; N, 3.08.

General Procedure for the Synthesis of 7a–d

Under Ar atmosphere, a mixture of 6-trifluoromethanesulfonyloxy-2*H*-isoquinolin-1-one derivative (**6a-c**)(2 mmol), trimethylstannyl derivative (**3a-c**)(4 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), and LiCl (0.3 g, 6 mmol) in dry 1,4-dioxane (20 mL) heated under reflux for 60 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with saturated Na_2CO_3 and brine, dried, and concentrated under reduced pressure.

3,6-Diphenyl-4-ethoxycarbonyl-8-hydroxy-2*H*-isoquinolin-1-one (7a)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ether, 1 : 2) to give 524 mg (68%) of **7a**, mp 238–240 °C (ethyl acetate). IR (KBr) cm^{-1}: 1711, 1646. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.1 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 7.19 (1H, d, *J* = 1.5 Hz), 7.38-7.67 (11H, m), 9.67 (1H, br s), 12.19 (1H, s). MS (*m/z*): 385 (M^+). *Anal.* Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 74.64; H, 5.11; N, 3.51.

4-Ethoxycarbonyl-8-hydroxy-3-phenyl-6-(3-pyridyl)-2*H*-isoquinolin-1-one (7b)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : ethyl acetate, 2 : 1) to give 541 mg (70%) of **7b**, mp 248–250 °C (ethyl acetate). IR (KBr) cm^{-1}: 1706, 1662. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.1 Hz), 4.09 (2H, q, *J* = 7.1 Hz), 7.14 (1H, d, *J* = 1.5 Hz), 7.40 (1H,

dd *J* = 7.9, 4.9 Hz), 7.52 (1H, d, *J* = 1.5 Hz), 7.54-7.58 (5H, m), 7.91-7.96 (1H, m), 8.64 (1H, dd, *J* = 4.8, 1.5 Hz), 8.87 (1H, d, *J* = 2.0 Hz), 10.87 (1H, br s), 12.19 (1H, s). MS (*m/z*): 386 (M^+). *Anal.* Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.62; H, 4.91; N, 7.12.

4-Ethoxycarbonyl-3-(4-fluorophenyl)-8-hydroxy-6-(3-pyridyl)-2*H*-isoquinolin-1-one (7c)

The crude product was purified by recrystallization from methanol to give 485 mg (60%) of **7c**, mp 243–245 °C. IR (KBr) cm^{-1}: 1707, 1665. ^{1}H-NMR (270 MHz, $CDCl_3$) □: 0.99 (3H, t, *J* = 7.1 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 7.16 (1H, d, *J* = 1.5 Hz), 7.21-7.28 (2H, m), 7.41 (1H, dd, *J* = 7.8, 4.5 Hz), 7.49 (1H, d, *J* = 1.5 Hz), 7.53-7.59 (2H, m), 7.91-7.95 (1H, m), 8.64 (1H, dd, *J* = 4.5, 1.5 Hz), 8.88 (1H, d, *J* = 1.9 Hz), 10.64 (1H, br s), 12.14 (1H, s). MS (*m/z*): 404 (M^+). *Anal.* Calcd for $C_{23}H_{17}N_2O_4F$: C, 68.31; H, 4.24; N, 6.93. Found: C, 68.03; H, 4.37; N, 7.22.

4-Ethoxycarbonyl-8-hydroxy-3-isopropyl-6-phenyl-2*H*-isoquinolin-1-one (7d)

The crude product was purified by recrystallization from acetone to give 492 mg (70%) of **7d**, mp 228–229 °C. IR (KBr) cm^{-1}: 1710, 1648. ^{1}H-NMR (270 MHz, $CDCl_3$) □: 1.37 (6H, d, *J* = 7.1 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 3.19-3.30 (1H, m), 4.46 (2H, q, *J* = 7.1 Hz), 7.14 (1H, d, *J* = 1.5 Hz), 7.26 (1H, d, *J* = 1.5 Hz), 7.37-7.50 (3H, m), 7.58-7.63 (2H, m), 9.38 (1H, br s), 12.36 (1H, s). MS (*m/z*): 351 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.58; H, 6.16; N, 3.78.

4-Ethoxycarbonyl-8-hydroxy-3-isopropyl-6-(2-pyridyl)-2*H*-isoquinolin-1-one (7e)

The crude product was purified by flash column chromatography on silica gel (*n*-hexane : diethyl ether, 1 : 3) to give 444 mg (63%) of **7e**, mp 247–249 °C (methanol). IR (KBr) cm^{-1}: 1720, 1648. ^{1}H-NMR (270 MHz, $CDCl_3$) □: 1.40 (6H, d, *J* = 7.1 Hz), 1.45 (3H, t, *J* = 7.1 Hz), 3.22-3.33 (1H, m), 4.49 (2H, q, *J* = 7.1 Hz), 7.25-7.32 (1H, m), 7.52 (1H, d, *J* = 1.5 Hz), 7.74-7.83 (3H, m), 8.71-8.74 (1H, m), 9.86 (1H, br s), 12.36 (1H, s). MS (*m/z*): 352 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.17; H, 5.86; N, 7.61.

4-Ethoxycarbonyl-8-hydroxy-3-isopropyl-6-(3-pyridyl)-2*H*-isoquinolin-1-one (7f)

The crude product was purified by recrystallization from acetone to give 507 mg (72%) of **7f**, mp 251–253 °C. IR (KBr) cm^{-1}: 1720, 1648. ^{1}H-NMR (270 MHz, $CDCl_3$) □: 1.40 (6H, d, *J* = 7.1 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 3.21-3.29 (1H, m), 4.47 (2H, q, *J* = 7.1 Hz), 7.11 (1H, d, *J* = 1.5 Hz), 7.26 (1H, d, *J* = 1.5 Hz), 7.40 (1H, dd, *J* = 7.9, 4.9 Hz), 7.88-7.93 (1H, m), 8.66 (1H, dd, *J* = 4.9, 1.6 Hz), 8.87 (1H, d, *J* = 2.3 Hz), 9.84 (1H, br s), 12.44 (1H, s). MS (*m/z*): 352 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.92; H, 6.01; N, 7.78.

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