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One-Pot Approach to 2,3-Disubstituted-2,3-dihydro-4-quinolones from 2-Alkynylbenzamides

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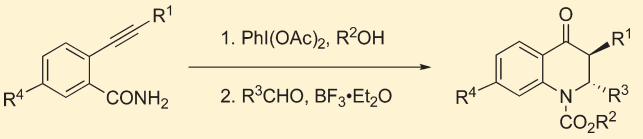
Supporting Information

ABSTRACT: Concise and efficient syntheses of various *trans*-2,3-disubstituted-2,3-dihydro-4-quinolones have been achieved via tandem Hofmann-type rearrangement of 2-alkynylbenzamides, nucleophilic addition of alcohols to the isocyanate intermediates, intermolecular [2+2]-cycloaddition with carbon−carbon triple bonds and aldehydes, and intramolecular aminocyclization of nitrogen of carbamates to the α,β-unsaturated ketones.



Numerous synthetic methodologies for quinolone syntheses have been reported[1] because the ring system constitutes a basic structural unit of a large number of natural products,[2] synthetic intermediates,[3] and bioactive molecules including antimitotic,[4] antiviral,[5] antibacterial,[6] and anticancer[7] agents and HIV-1 integrase inhibitors.[8] Similarly, 2,3-dihydro-4-quinolones possess attractive pharmacological properties[9] and also are used as important synthetic intermediates for the biologically active compounds.[10,11] As part of our continuing interest in the syntheses of biologically active compounds using a tandem strategy, we have recently reported a procedure for the one-pot platinum(II)-catalyzed synthesis of indoles and isoquinolines via isocyanates, which were derived from a Hofmann-type rearrangement of amides **1** using a hypervalent iodine reagent.[12] A significant feature of this strategy is that relatively stable alkynylamides could be used as a starting material to efficiently furnish the indoles and isoquinolines in combination with the Hofmann-type rearrangement. As an extension of this approach, we now report our successful stereoselective synthesis of *trans*-2,3-dihydro-4-quinolones **4** featuring a tandem strategy that involves (1) Hofmann-type rearrangement of 2-alkynylbenzamides **1** followed by a nucleophilic addition of an alcohol to an isocyanate intermediate (**1** → **2**), (2) acid-catalyzed intermolecular [2+2]-cycloaddition with carbon−carbon triple bonds of carbamates **2** and aldehydes (**2** → **3**), and (3) acid-catalyzed intramolecular aminocyclization to the α,β-unsaturated ketones (**3** → **4**) (Scheme 1).

A key to the success of this approach is whether an acid catalyst, required for the [2+2]-cycloaddition[13,14] and the aminocyclization, can tolerate the presence of coproducts generated in the Hofmann-type rearrangement by the hypervalent iodine reagent. To explore this possibility, we examined the reaction using **1a**, readily available from Sonogashira coupling of 2-iodobenzamide and 1-hexyne, as a substrate (Table 1). After the treatment of **1a** with EtOH (4 equiv) in the presence of hypervalent iodine (1 equiv) at 60 °C for 2 h, which is a procedure required to ensure the completion of the Hofmann-type rearrangement, benzaldehyde (1.5 equiv) and a Brønsted or Lewis acid catalyst were added. Without the addition of an external acid (Table 1, entry 1) and with $Cu(OTf)_2$ (Table 1, entry 2), the reaction stopped at the carbamate stage to give only **2a**. Most of the other acids afforded the desired quinolone derivative **4a** with high trans-selectivity together with **2a** and ketone **5a**,[15] presumably produced from the acetic acid-catalyzed hydrolysis of alkyne **2a**, with various yields and in variable ratios. The best result was obtained with $PhI(OCOCH_3)_2$ and $BF_3 \cdot Et_2O$ (1 equiv), which afforded **4a** in 73% yield with high trans-selectivity (Table 1, entry 7).

Having in hand the optimized conditions for the formation of **4a**, we further explored the scope of this reaction, particularly in regard to the substituents R^1 and R^4, alcohol R^2OH, and aldehyde R^3CHO (Table 2). In most cases, moderate yields and high trans-selectivities of 2,3-disubstituted-2,3-dihydro-4-quinolones **4**[16] were observed. In the presence of either electron-donating or moderately electron-withdrawing substituents R^4 on the aromatic ring of 2-alkynylbenzamides **1**, the yields of desired products **4** ranged from 72−81% (Table 2, entries 1−3). However, the presence of the strongly electron-withdrawing nitro group on the aromatic ring slowed the [2+2]-cycloaddition reaction, giving carbamate **2e** exclusively (Table 2, entry 4). The use of benzyl alcohol as the nucleophile afforded only *N*-Cbz-protected 4-quinolone **4f** (Table 2, entry 5). When aliphatic aldehydes were used, 4-quinolones were also obtained with high trans-selectivities (Table 2, entries 10 and 11). 2-Alkynylbenzamides **1**, bearing an aromatic substituent on the terminus of the alkyne, also gave the corresponding 4-quinolone **4** in good yields (Table 2, entries 14 and 15). When *p*-cyanobenzaldehyde or *p*-

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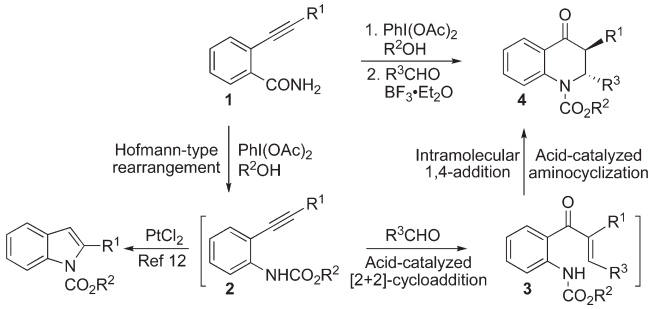
nitrobenzaldehyde were used as the aldehyde at 60 °C, intermolecular [2+2]-cycloaddition proceeded stereoselectively to give only the corresponding trisubstituted enones **3q** or **3r** with high (E)-selectivity[13] accompanied by ketone **5a** (Table 2, entries 16 and 18). The configuration of the enone double bond of **3** was assigned on the basis of NOESY experiments. Fortunately, the same reactions at 90 °C gave the desired 4-quinolones **4q** and **4r** in high yields with trans-selectivities (Table 2, entries 17 and 19). To determine whether the trans-selectivity of the formation of **4** depends on the *E*:*Z*-configuration of enone **3**, we undertook the following experiment (Scheme 2). The stereoisomeric mixture of the enone **3q** (*E*:*Z* = 3:1) was derived from the enone **3q** (*E*:*Z* = 25:1, Table 2, entry 16) after being stored at room temperature for five months. Following the addition of $BF_3 \cdot Et_2O$ (1 equiv) in DCE and stirring of the mixture at 90 °C for 24 h, the reaction afforded only *trans*-**4q** in 80% yield. Thus, the predominant *trans*-**4q** formation is not dependent on the *E*:*Z*-configuration of **3q**, and is presumably produced from normal 1,4-addition of carbamate nitrogen to α,β-unsaturated carbonyl compound **3**. Terminal alkyne **1f** was also suitable for this reaction to afford **4s** (Table 2, entry 20). This reaction can be easily conducted on a scale of 7 mmol of **1f** (1.015 g) in a slightly higher yield (Table 2, entry 21). The reaction with benzophenone instead of aldehydes failed to give any of the desired cyclic compound **4t** at all (Table 2, entry 22).

In conclusion, we have demonstrated the synthesis of various *trans*-2,3-disubstituted-2,3-dihydro-4-quinolones from 2-alkynylbenzamide derivatives by a one-pot tandem process that involves a Hofmann-type rearrangement of 2-alkynylbenzamides, a nucleophilic addition of alcohols to the resulting isocyanate intermediates, an intermolecular [2+2]-cycloaddition with an alkyne triple bond and aldehydes, and an intramolecular aminocyclization to the α,β-unsaturated ketones.

Scheme 1. One-Pot Synthesis of 2,3-Disubstituted-2,3-dihydro-4-quinolones 4 from Amides 1

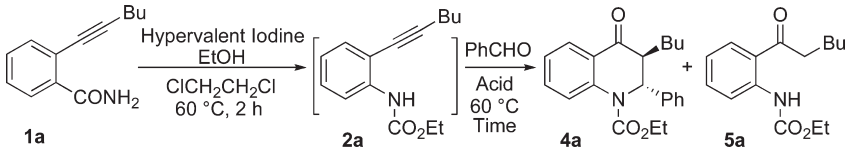


EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer. Chemical shifts are reported in δ (ppm) from tetramethylsilane as an internal standard. Data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). Infrared spectra were obtained using an FT spectrometer. Analytical thin layer chromatography was performed on Merck silica gel 60 F254 TLC plates. Compouds **1a**,[17] **1e**,[17] **2a**,[13d] **4a**,[13d] **4l**,[13d] **4r**,[13d] and **5a**[13d] are all known compounds. Experimental procedures and data for compounds **1b**, **1c**, **1d**, and **1f** have been reported in our previous paper.[12a]

Ethyl 2-(Hex-1-ynyl)5-nitrophenylcarbamate (2e). White solid (56 mg, 97%): mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 9.05 (1H, s), 7.81 (1H, dd, *J* = 8.4, 2.4 Hz), 7.50 (1H, s), 7.45 (1H, d, *J* = 8.4 Hz), 4.29 (2H, q, *J* = 7.3 Hz), 2.56 (2H, t, *J* = 7.2 Hz), 1.69−1.64 (2H, m), 1.55−1.49 (2H, m), 1.36 (3H, t, *J* = 7.3 Hz), 0.99 (3H, t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 152.8, 147.5, 139.8, 131.9, 118.1, 116.9, 112.2, 103.0, 74.7, 61.9, 30.3, 22.0, 19.4, 14.4, 13.5; IR ($CHCl_3$, cm^{-1}) 3398, 3035,

Table 1. Optimization of the Reaction Conditions[a]



entry	hypervalent iodine	acid (1 equiv)	time (h)	**4a** (%)[b] (trans:cis)[c]	**5a** (%)	**2a** (%)
1	$PhI(OCOCF_3)_2$		20	trace	5	48
2	$PhI(OCOCF_3)_2$	$Cu(OTf)_2$	20	0	0	64
3	$PhI(OCOCF_3)_2$	$BF_3 \cdot Et_2O$	20	60 (20:1)	0	0
4	$PhI(OCOCF_3)_2$	$AgSbF_6$	20	43 (18:1)	4	0
5	$PhI(OCOCH_3)_2$	SbF_5	24	trace	4	4
6	$PhI(OCOCH_3)_2$	AgOTf	24	5 (20:1)	5	10
7	$PhI(OCOCH_3)_2$	$BF_3 \cdot Et_2O$	18	73 (40:1)	0	0
8	$PhI(OCOCH_3)_2$	$BF_3 \cdot Et_2O$ (0.5 equiv)	18	48 (28:1)	9	12
9	$PhI(OCOCH_3)_2$	$BF_3 \cdot Et_2O$ (0.1 equiv)	24	15 (27:1)	8	35
10	$PhI(OCOCH_3)_2$	TfOH	24	8 (27:1)	4	8
11	$PhI(OCOCH_3)_2$	$In(OTf)_3$	24	18 (24:1)	27	0
12	PhI(OTs)(OH)	$BF_3 \cdot Et_2O$	20	32 (18:1)	4	0

[a] Amide (0.2 mmol), hypervalent iodine (0.2 mmol), EtOH (0.8 mmol), benzaldehyde (0.3 mmol), and acid (0.2 mmol) in $ClCH_2CH_2Cl$ (1 mL) were used except in entries 8 and 9. [b] Isolated yields. [c] Ratios were determined by ^{1}H NMR analysis.

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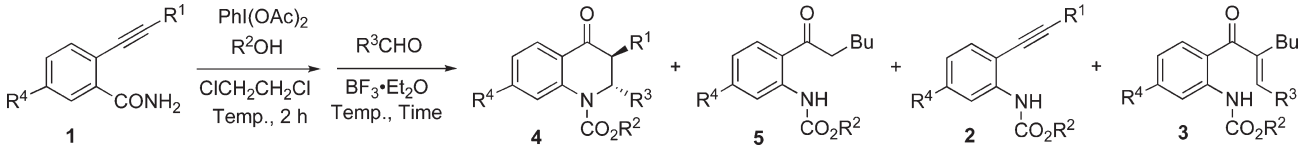
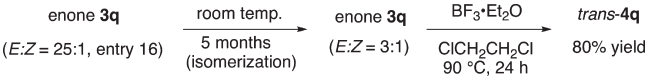
Table 2. One-Pot Synthesis of 4-Quinolone 4 from Benzamide 1



entry	alkyne	R^1	R^2	R^3	R^4	temp (°C)	time (h)	4	(trans:cis) (%)	5 (%)	2 or 3 (*E*:*Z*) (%)
1	**1a**	Bu	Et	*p*-MeC_6H_4	H	60	20	**4b**	81 (22:1)	0	0
2	**1b**	Bu	Et	*p*-MeC_6H_4	OMe	60	16	**4c**	72 (7:1)	0	0
3	**1c**	Bu	Et	*p*-MeC_6H_4	F	60	16	**4d**	80 (38:1)	**5d** 7	0
4	**1d**	Bu	Et	*p*-MeC_6H_4	NO_2	60	24	**4e**	0	0	**2e** 97
5	**1a**	Bu	Bn	*p*-MeC_6H_4	H	60	20	**4f**	73 (8:1)	0	0
6	**1a**	Bu	Et	*o*-MeC_6H_4	H	60	20	**4g**	82 (20:1)	0	0
7	**1a**	Bu	Et	*m*-MeC_6H_4	H	60	20	**4h**	76 (33:1)	0	0
8	**1a**	Bu	Et	*p*-$MeOC_6H_4$	H	60	24	**4i**	68 (98:1)	0	0
9	**1a**	Bu	Et	*p*-FC_6H_4	H	60	20	**4j**	76 (25:1)	0	0
10	**1a**	Bu	Et	hexyl	H	60	20	**4k**	61 (20:1)	23	0
11	**1a**	Bu	Et	cyclohexyl	H	60	20	**4l**	87 (99:1)	0	0
12	**1a**	Bu	Me	Ph	H	60	20	**4m**	72 (28:1)	0	0
13	**1b**	Bu	Et	Ph	OMe	60	20	**4n**	52 (11:1)	0	0
14	**1e**	Ph	Me	*p*-MeC_6H_4	H	60	16	**4o**	73 (trans)	0	0
15	**1e**	Ph	Et	*p*-MeC_6H_4	H	60	16	**4p**	66 (trans)	0	0
16	**1a**	Bu	Et	*p*-CNC_6H_4	H	60	32	**4q**	0	**5a** 19	**3q** 55 (25:1)
17	**1a**	Bu	Et	*p*-CNC_6H_4	H	90	24	**4q**	82 (trans)	0	0
18	**1a**	Bu	Et	*p*-$NO_2C_6H_4$	H	60	24	**4r**	0	**5a** 24	**3r** 59 (25:1)
19	**1a**	Bu	Et	*p*-$NO_2C_6H_4$	H	90	24	**4r**	80 (trans)	0	0
20	**1f**	H	Et	*p*-MeC_6H_4	H	60	20	**4s**	85	0	0
21[a]	**1f**	H	Et	*p*-MeC_6H_4	H	60	20	**4s**	88	0	0
22	**1a**	Bu	Et	(PhCOPh)	H	90	22	**4t**	0	**5a** trace	0

[a] The reaction was conducted with a 7 mmol (1.015 g) scale of **1f**.

Scheme 2. Conversion of Enone 3q to *trans*-4q



1738, 1533, 1347, 1237, 1197, 819. MS (EI): m/z = 290 (M^+). HRMS (EI): m/z calcd for $C_{15}H_{18}N_2O_4$: 290.1267; found: 290.1274.

(*E*)-Ethyl 2-(2-(4-Cyanobenzylidene)hexanoyl)phenylcarbamate (3q). Pale yellow oil (41 mg, 55%): ^{1}H NMR ($CDCl_3$) δ 10.10 (1H, s), 8.41 (1H, d, J = 8.9 Hz), 7.70−7.69 (3H, m), 7.56 (1H, t, J = 7.9 Hz), 7.44 (2H, d, J = 7.6 Hz), 7.06 (1H, t, J = 7.9 Hz), 6.81 (1H, s), 4.24 (2H, q, J = 6.9 Hz), 2.68 (2H, t, J = 7.9 Hz), 1.54−1.49 (2H, m), 1.42−1.31 (5H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 201.2, 153.8, 145.6, 141.1, 140.1, 136.0, 134.3, 132.7, 132.3, 129.5, 123.0, 121.2, 120.0, 118.5, 111.8, 61.3, 30.6, 28.1, 22.9, 14.5, 13.8; IR ($CHCl_3$, cm^{-1}) 3230, 3034, 3009, 1728, 1630, 1582, 1524, 1449, 1238, 683. MS (EI): m/z = 376 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{24}N_2O_3$: 376.1787; found: 376.1780.

(*E*)-Ethyl 2-(2-(4-Nitrobenzylidene)hexanoyl)phenylcarbamate (3r). Pale yellow oil (47 mg, 59%): ^{1}H NMR ($CDCl_3$) δ 10.13 (1H, s), 8.42 (1H, d, J = 8.2 Hz), 8.27 (2H, d, J = 8.6 Hz), 7.71 (1H, d, J = 7.6 Hz), 7.57 (1H, t, J = 7.9 Hz), 7.50 (2H, d, J = 8.6 Hz), 7.07 (1H, t, J = 7.6 Hz), 6.85 (1H, s), 4.24 (2H, q, J = 6.9 Hz), 2.70 (2H, t, J = 7.9 Hz), 1.54−1.51 (2H, m), 1.41−1.37 (2H, m), 1.33 (3H, t, J = 6.9 Hz), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 201.1, 153.8, 147.2, 146.1, 142.0, 141.1, 135.3, 134.4, 132.7, 129.7, 123.8, 122.8, 121.2, 120.1, 61.3, 30.6, 28.2, 22.9, 14.5, 13.8; IR ($CHCl_3$, cm^{-1}) 3277, 3036, 3009, 1730, 1632, 1599, 1582, 1528, 1516, 1449, 1346, 1250, 1196, 1163, 1059. MS (EI): m/z = 396 (M^+). HRMS (EI): m/z calcd for $C_{22}H_{24}N_2O_5$: 396.1685; found: 396.1689.

General Procedure for One-Pot Synthesis of 2,3-Disubstituted-2,3-dihydro-4-quinolones 4 from 2-Alkynylbenzamides 1. To a solution of 2-alkynylbenzamide **1** (0.20 mmol) and $PhI(OAc)_2$ (0.22 mmol) in 1,2-dichloroethane (1.0 mL) was added alcohol (0.80 mmol), and the mixture was stirred at 60 °C for 2 h. Then, aldehyde (0.30 mmol) and $BF_3 \cdot Et_2O$ (0.20 mmol) was added, and the mixture was stirred at 60 or 90 °C for 16−32 h. After the completion of the reaction was confirmed by TLC, the reaction mixture was directly chromatographed on silica gel using hexane: ethyl acetate (10:1 to 5:1) as an eluent to afford the 2,3-disubstituted-2,3-dihydro-4-quinolone **4**.

Ethyl 3-Butyl-4-oxo-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4b). Pale yellow oil (59 mg, 81%): ^{1}H NMR ($CDCl_3$) δ 7.90−7.89 (2H, m), 7.47 (1H, t, J = 7.9 Hz), 7.08−7.04 (3H, m), 7.00 (2H, d, J = 7.6 Hz), 5.98 (1H, s), 4.46−4.32 (2H, m), 3.12 (1H, t, J = 7.6 Hz), 2.22 (3H, s), 1.81−1.71 (2H, m), 1.62−1.54 (1H, m), 1.50−1.43 (1H, m), 1.41−1.34 (5H, m), 0.92 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 195.9, 155.1, 141.1, 137.0, 135.3, 134.4, 129.2, 129.1, 127.3, 126.5, 123.8, 123.5, 62.7, 59.6, 51.1, 29.7, 29.2, 22.5, 20.8, 14.5, 13.8; IR ($CHCl_3$, cm^{-1}) 3036, 3007, 2961, 2932, 1706, 1682, 1601, 1479, 1460, 1396, 1381, 1321, 1298, 1269, 1242, 1196, 1049. MS (EI): m/z = 365 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{27}NO_3$: 365.1991; found: 365.1991.

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Ethyl 3-Butyl-7-methoxy-4-oxo-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4c). Pale yellow oil (57 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, d, J = 8.9 Hz), 7.39 (1H, s), 7.00 (2H, d, J = 8.2 Hz), 6.94 (2H, d, J = 8.2 Hz), 6.55 (1H, dd, J = 8.6, 2.4 Hz), 5.89 (1H, s), 4.38−4.23 (2H, m), 3.76 (3H, s), 2.98−2.95 (1H, m), 2.16 (3H, s), 1.68−1.27 (9H, m), 0.84 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 194.8, 164.6, 155.0, 143.0, 137.1, 135.7, 129.4, 129.3, 126.5, 117.4, 111.1, 107.8, 62.8, 59.9, 55.5, 50.9, 30.0, 29.3, 22.6, 20.9, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1706, 1696, 1603, 1447, 1310, 1272. MS (EI): m/z = 395 (M^+). HRMS (EI): m/z calcd for $C_{24}H_{29}NO_4$: 395.2097; found: 395.2091.

Ethyl 3-Butyl-7-fluoro-4-oxo-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4d). Pale yellow oil (61 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 7.91 (1H, t, J = 7.6 Hz), 7.72 (1H, d, J = 10.3 Hz), 7.04 (4H, q, J = 7.8 Hz), 6.77 (1H, td, J = 8.2, 1.8 Hz), 5.97 (1H, s), 4.45−4.34 (2H, m), 3.09 (1H, t, J = 7.2 Hz), 2.24 (3H, s), 1.76−1.69 (2H, m), 1.59−1.54 (1H, m), 1.47−1.34 (6H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 194.5, 167.2, 165.6, 154.7, 143.2, 143.1, 137.3, 135.1, 130.1, 130.0, 129.4, 126.4, 120.0, 111.7, 111.6, 110.6, 110.4, 63.1, 59.9, 50.8, 29.7, 29.2, 22.5, 20.9, 14.4, 13.9; IR ($CHCl_3$, cm^{-1}) 3037, 3008, 2962, 2933, 1711, 1684, 1610, 1585, 1487, 1443, 1397, 1381, 1305, 1266. MS (EI): m/z = 383 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{26}NO_3F$: 383.1897; found: 383.1888.

Benzyl 3-Butyl-4-oxo-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4f). Pale yellow oil (62 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d, J = 6.9 Hz), 7.46 (1H, t, J = 7.6 Hz), 7.40−7.34 (5H, m), 7.08−7.05 (3H, m), 6.99 (2H, d, J = 7.6 Hz), 5.97 (1H, s), 5.43 (1H, d, J = 12.4 Hz), 5.29 (1H, d, J = 12.4 Hz), 3.08 (1H, t, J = 7.6 Hz), 2.22 (3H, s), 1.70−1.66 (2H, m), 1.48−1.45 (1H, m), 1.40−1.35 (1H, m), 1.30−1.24 (2H, m), 0.85 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 195.8, 155.0, 141.0, 137.2, 135.7, 135.3, 134.5, 129.3, 128.7, 128.5, 128.3, 127.4, 126.6, 124.0, 123.8, 123.6, 68.4, 60.0, 51.1, 29.8, 29.2, 22.5, 20.9, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 2960, 1706, 1684, 1602, 1480, 1461, 1389, 1339, 1321, 1297, 1268, 1021. MS (EI): m/z = 427 (M^+). HRMS (EI): m/z calcd for $C_{28}H_{29}NO_3$: 427.2147; found: 427.2142.

Ethyl 3-Butyl-4-oxo-2-*o*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4g). White solid (60 mg, 82%): mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.98−7.95 (2H, m), 7.55−7.52 (1H, m), 7.16−7.06 (3H, m), 6.90 (1H, t, J = 7.6 Hz), 6.82 (1H, d, J = 8.2 Hz), 6.07 (1H, s), 4.38−4.24 (2H, m), 2.85 (1H, t, J = 7.2 Hz), 2.41 (3H, s), 1.80−1.72 (2H, m), 1.63−1.58 (1H, m), 1.47−1.30 (6H, m), 0.91 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 196.1, 154.8, 142.3, 137.3, 135.5, 134.7, 131.2, 127.6, 127.4, 126.1, 125.7, 123.8, 123.6, 123.3, 62.8, 58.4, 51.6, 30.9, 29.2, 22.6, 19.6, 14.4, 13.9; IR ($CHCl_3$, cm^{-1}) 3038, 3007, 1702, 1698, 1693, 1681, 1674, 1601, 1480, 1460, 1373, 1320, 1295, 1270. MS (EI): m/z = 365 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{27}NO_3$: 365.1991; found: 365.1997.

Ethyl 3-Butyl-4-oxo-2-*m*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4h). Pale yellow oil (55 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 7.89 (2H, dd, J = 7.9, 1.7 Hz), 7.50−7.47 (1H, m), 7.09−7.06 (2H, m), 7.00 (1H, s), 6.97−6.95 (2H, m), 5.98 (1H, s), 4.45−4.42 (1H, m), 4.36−4.33 (1H, m), 3.15−3.12 (1H, m), 2.23 (3H, s), 1.79−1.73 (2H, m), 1.60−1.57 (1H, m), 1.49−1.45 (1H, m), 1.41−1.36 (5H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 195.9, 155.1, 141.3, 138.4, 138.2, 134.5, 128.5, 128.2, 127.5, 127.4, 123.8, 123.7, 123.6, 62.8, 59.8, 51.2, 29.8, 29.3, 22.5, 21.5, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3038, 3008, 1700, 1686, 1681, 1602, 1480, 1461, 1380, 1322, 1297, 1269. MS (EI): m/z = 365 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{27}NO_3$: 365.1991; found: 365.1989.

Ethyl 3-Butyl-2-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (4i). Pale yellow oil (52 mg, 68%): ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, dd, J = 7.6, 1.4 Hz), 7.85 (1H, d, J = 7.6 Hz), 7.47 (1H, td, J = 7.9, 1.8 Hz), 7.12−7.06 (3H, m), 6.73 (2H, d, J = 8.2 Hz), 5.96 (1H, s), 4.45−4.34 (2H, m), 3.70 (3H, s), 3.11−3.08 (1H, m), 1.77−1.72 (2H, m), 1.61−1.55 (1H, m), 1.49−1.44 (1H, m), 1.39−1.35 (5H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 196.1, 158.7, 155.1, 141.1, 134.5, 130.4, 127.9, 127.4, 123.8, 123.5, 113.9, 62.8, 59.4, 55.2, 51.1, 29.7, 29.3, 22.5, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 2961, 2934, 1682, 1601, 1514, 1479, 1462, 1396, 1381, 1321, 1298, 1271, 1252, 1034, 714. MS (EI): m/z = 381 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{27}NO_4$: 381.1940; found: 381.1935.

Ethyl 3-Butyl-2-(4-fluorophenyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (4j). Pale yellow oil (56 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 7.90 (1H, d, J = 7.6 Hz), 7.85 (1H, d, J = 7.6 Hz), 7.49 (1H, t, J = 7.9 Hz), 7.18−7.15 (2H, m), 7.09 (1H, t, J = 7.6 Hz), 6.89 (2H, t, J = 8.6 Hz), 5.98 (1H, s), 4.47−4.33 (2H, m), 3.11−3.08 (1H, m), 1.81−1.71 (2H, m), 1.62−1.53 (1H, m), 1.50−1.43 (1H, m), 1.41−1.34 (5H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 195.7, 162.8, 161.1, 155.1, 140.9, 134.6, 134.3, 134.3, 128.4, 128.4, 127.5, 124.0, 123.8, 123.4, 115.6, 115.5, 63.0, 59.4, 51.2, 29.8, 29.2, 22.5, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1684, 1602, 1512, 1480, 1461, 1380, 1323, 1297, 1269, 1163. MS (EI): m/z = 369 (M^+). HRMS (EI): m/z calcd for $C_{22}H_{24}NO_3F$: 369.1740; found: 369.1732.

Ethyl 3-Butyl-2-hexyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (4k). Pale yellow oil (44 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, dd, J = 7.9, 1.7 Hz), 7.81 (1H, br), 7.54−7.51 (1H, m), 7.15 (1H, t, J = 7.2 Hz), 4.79−4.77 (1H, m), 4.36−4.28 (2H, m), 2.45−2.42 (1H, m), 1.61−1.54 (3H, m), 1.51−1.46 (1H, m), 1.43−1.17 (15H, m), 0.92−0.82 (6H, m); ^{13}C NMR ($CDCl_3$) δ 196.7, 154.9, 140.5, 134.3, 127.3, 124.2, 123.8, 123.5, 62.4, 57.5, 52.2, 31.6, 31.6, 29.5, 29.2, 28.8, 26.1, 22.5, 14.5, 14.0, 13.9; IR ($CHCl_3$, cm^{-1}) 3037, 3009, 1680, 1601, 1539, 1521, 1506, 1480, 1461, 1374, 1321, 1295. MS (EI): m/z = 359 (M^+). HRMS (EI): m/z calcd for $C_{22}H_{33}NO_3$: 359.2460; found: 359.2463.

Methyl 3-Butyl-4-oxo-2-phenyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4m). Pale yellow oil (49 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 7.90 (2H, dd, J = 7.9, 1.7 Hz), 7.51−7.48 (1H, m), 7.22−7.14 (5H, m), 7.09 (1H, t, J = 7.6 Hz), 6.00 (1H, s), 3.93 (3H, s), 3.13 (1H, td, J = 7.6, 2.1 Hz), 1.80−1.74 (2H, m), 1.60−1.56 (1H, m), 1.49−1.45 (1H, m), 1.41−1.36 (2H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 195.7, 155.6, 141.1, 138.3, 134.6, 128.6, 127.5, 126.6, 124.0, 123.6, 123.5, 60.2, 53.7, 51.2, 29.8, 29.2, 22.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1715, 1706, 1684, 1480, 1441. MS (EI): m/z = 337 (M^+). HRMS (EI): m/z calcd for $C_{21}H_{23}NO_3$: 337.1678; found: 337.1670.

Ethyl 3-Butyl-7-methoxy-4-oxo-2-phenyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4n). Pale yellow oil (40 mg, 52%): ^{1}H NMR ($CDCl_3$) δ 7.85 (1H, d, J = 8.9 Hz), 7.48 (1H, s), 7.25−7.15 (5H, m), 6.63 (1H, dd, J = 8.9, 2.1 Hz), 5.99 (1H, s), 4.47−4.42 (1H, m), 4.36−4.31 (1H, m), 3.85 (3H, s), 3.07−3.05 (1H, m), 1.77−1.72 (2H, m), 1.60−1.56 (1H, m), 1.49−1.43 (1H, m), 1.40−1.34 (5H, m), 0.92 (3H, t, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 194.6, 164.6, 155.0, 143.0, 138.7, 129.5, 128.6, 127.4, 126.6, 117.4, 111.1, 107.7, 62.8, 60.1, 55.5, 50.9, 30.0, 29.3, 22.5, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1706, 1700, 1675, 1603, 1498, 1448, 1311, 1271. MS (EI): m/z = 381 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{27}NO_4$: 381.1940; found: 381.1940.

Methyl 4-Oxo-3-phenyl-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4o). White solid (54 mg, 73%): mp 131−132 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, dd, J = 7.9, 1.7 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.53 (1H, t, J = 7.9 Hz), 7.31−7.13 (8H, m), 7.05 (2H, d, J = 8.2 Hz), 6.13 (1H, s), 4.42 (1H, d, J = 1.4 Hz), 3.62 (3H, s), 2.25 (3H, s); ^{13}C NMR ($CDCl_3$) δ 193.6, 155.3, 141.9, 137.4, 137.3, 135.2, 135.0, 129.4, 129.0, 127.7, 127.7, 127.4, 126.6, 125.0, 124.4, 124.2, 62.6, 56.1, 53.4, 20.9; IR ($CHCl_3$, cm^{-1}) 3035, 1718, 1684, 1603, 1481, 1441, 1330, 1306. MS (EI): m/z = 371 (M^+). HRMS (EI): m/z calcd for $C_{24}H_{21}NO_3$: 371.1521; found: 371.1523.

Ethyl 4-Oxo-3-phenyl-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4p). Pale yellow oil (51 mg, 66%): ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, J = 7.6 Hz), 7.82 (1H, d, J = 8.2 Hz), 7.52 (1H, t, J = 7.6 Hz), 7.30−7.12 (8H, m), 7.05 (2H, d, J = 7.6 Hz), 6.14 (1H, s), 4.43 (1H, s), 4.12−4.05 (2H, m), 2.25 (3H, s), 1.04 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 193.8, 154.8, 142.0, 137.4, 137.4, 135.3, 134.9, 129.4, 129.0, 127.8, 127.6, 127.3, 126.7, 125.1, 124.6, 124.1, 62.5, 56.0, 20.9, 14.2; IR

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($CHCl_3$, cm^{-1}) 3037, 3009, 1710, 1684, 1602, 1481, 1461, 1396, 1323, 1302. MS (EI): m/z = 385 (M^+). HRMS (EI): m/z calcd for $C_{25}H_{23}NO_3$: 385.1678; found: 385.1683.

Ethyl 3-Butyl-2-(4-cyanophenyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (4q). White solid (62 mg, 82%): mp 137−138 °C; ^1H NMR ($CDCl_3$) δ 7.89 (1H, dd, J = 7.9, 1.7 Hz), 7.87 (1H, d, J = 8.9 Hz), 7.54−7.51 (3H, m), 7.31 (2H, d, J = 8.9 Hz), 7.12 (1H, t, J = 7.6 Hz), 6.04 (1H, s), 4.46−4.43 (1H, m), 4.38−4.36 (1H, m), 3.11 (1H, td, J = 7.6, 2.1 Hz), 1.80−1.75 (2H, m), 1.59−1.56 (1H, m), 1.49−1.45 (1H, m), 1.41−1.36 (5H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 194.9, 154.9, 144.1, 140.8, 134.9, 132.5, 127.6, 127.5, 124.3, 123.7, 123.2, 118.3, 111.6, 63.2, 59.8, 51.1, 29.7, 29.2, 22.5, 14.5, 13.9; IR ($CHCl_3$, cm^{-1}) 3037, 3009, 1715, 1685, 1602, 1480, 1462, 1378, 1322, 1296. MS (EI): m/z = 376 (M^+). HRMS (EI): m/z calcd for $C_{23}H_{24}N_2O_3$: 376.1787; found: 376.1780.

Ethyl 4-Oxo-2-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (4s). White solid (53 mg, 85%): mp 114−115 °C; ^1H NMR ($CDCl_3$) δ 7.89 (1H, dd, J = 7.6, 1.4 Hz), 7.79 (1H, d, J = 8.2 Hz), 7.47−7.44 (1H, m), 7.09−7.05 (3H, m), 7.01 (2H, d, J = 8.2 Hz), 6.18 (1H, s), 4.42−4.34 (2H, m), 3.30−3.29 (2H, m), 2.22 (3H, s), 1.38 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 193.0, 154.5, 141.7, 137.2, 135.2, 134.5, 129.3, 126.8, 126.5, 125.0, 124.4, 124.0, 62.9, 55.8, 42.4, 20.9, 14.5; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1685, 1603, 1481, 1462, 1397, 1381, 1269. MS (EI): m/z = 309 (M^+). HRMS (EI): m/z calcd for $C_{19}H_{19}NO_3$: 309.1365; found: 309.1364.

Ethyl 5-Fluoro-2-hexanoylphenylcarbamate (5d). Pale yellow oil (4 mg, 7%): ^1H NMR ($CDCl_3$) δ 11.45 (1H, br), 8.29 (1H, dd, J = 12.4, 2.7 Hz), 7.91 (1H, dd, J = 8.9, 6.2 Hz), 6.75−6.71 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 2.96 (2H, t, J = 7.2 Hz), 1.73−1.71 (2H, m), 1.38−1.34 (4H, m), 1.32 (3H, t, J = 7.2 Hz), 0.92 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 203.4, 167.1, 153.8, 144.3, 144.2, 133.3, 133.3, 117.8, 108.6, 108.5, 106.3, 106.1, 61.4, 39.9, 31.4, 24.3, 22.5, 14.4, 13.9; IR ($CHCl_3$, cm^{-1}) 3036, 3009, 1730, 1653, 1591, 1529, 1458, 1251. MS (EI): m/z = 281 (M^+). HRMS (EI): m/z calcd for $C_{15}H_{20}NO_3F$: 281.1427; found: 281.1428.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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