Ethyl 1,4-Dihydro-4-oxo-3-quinolinecarboxylates by a Tandem Addition-Elimination-S_NAr Reaction

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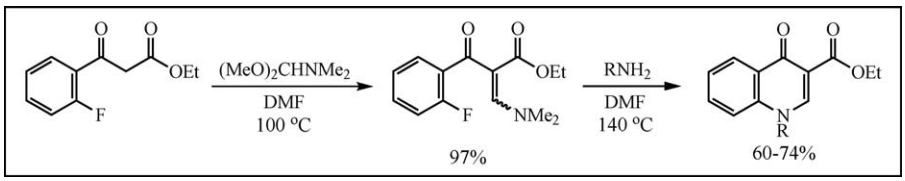

The ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylate ring structure, important in several drug compounds, has been prepared in two steps from ethyl 2-(2-fluorobenzoyl)acetate. Treatment of this β-ketoester with *N*,*N*-dimethylformamide dimethyl acetal gives a 97% yield of the 2-dimethylaminomethylene derivative. Reaction of this β-enaminone with primary amines in *N*,*N*-dimethylformamide at 140°C for 48 h then affords the 1,4-dihydro-4-oxo-3-quinolinecarboxylate esters in 60–74% yields by a tandem addition-elimination-S_NAr reaction. The synthesis of the starting material as well as procedural details and a mechanistic scenario are presented.

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INTRODUCTION

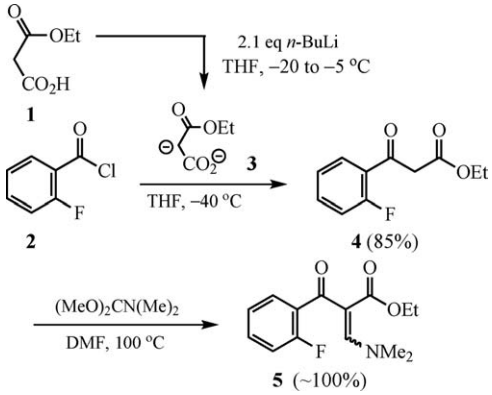
Compounds based on the 1,4-dihydro-4-oxo-3-quinolinecarboxylate scaffold are known to have significant biological activity. In particular, these compounds have proven valuable as antibiotics [1] and, more recently, as anti-ischemic agents for the treatment of heart attack and stroke victims [2]. Recently, we reported an approach to the syntheses of this ring system that involved a tandem reduction-addition-elimination reaction from an enaminone substrate, but this route proved to be quite limited in scope [3]. The current project sought to develop an alternative synthesis of these heterocycles involving a tandem addition-elimination-S_NAr reaction using a similar enaminone substrate.

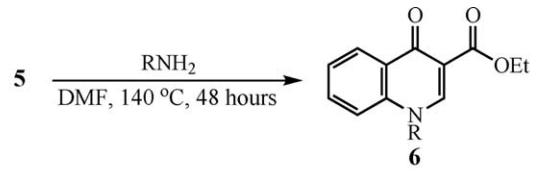
Earlier syntheses [4] of *N*-substituted 1,4-dihydro-4-oxo-3-quinolinecarboxylate esters have generally followed two strategies. In the first, conjugate addition of aniline to diethyl (ethoxymethylene)malonate to give a β-enamino diester was followed by thermal ring closure at 250°C and *N*-alkylation (overall yield *ca*. 50%). The disadvantage of this method is the high temperature used for the cyclization reaction, and the highly variable yields in the final alkylation [4,5]. For *N*-aryl cases, where alkylation by an S_N2 reaction is not possible, diphenylamine (the only case reported) was used to prepare the initial β-enamino diester [6]. The yield for this reaction was not given, but this procedure would require the use of symmetrical diarylamines to avoid mixtures in the cyclization step. A second approach to these compounds involved addition of a primary amine to ethyl propiolate to give an β-enamino monoester, acylation with a 2-fluorobenzoyl chloride derivative and ring closure by an S_NAr reaction using potassium carbonate in *N*,*N*-dimethylformamide (DMF) [2]. The combined yield for this sequence was generally lower than that for the two-step procedure described in this article.

RESULTS AND DISCUSSION

The synthesis of our cyclization substrates is summarized in Scheme 1. The fluoro-substituted compound was targeted because fluorine is the most reactive halogen in nucleophilic aromatic substitutions, especially for compounds bearing only modest electron-withdrawing groups [7,8]. Ethyl hydrogen malonate (**1**) [9] was converted to

Scheme 1. Synthesis of cyclization substrates.





	R	Yield (%)
a	*c*-C_3H_5–	68
b	*c*-C_6H_{11}–	60
c	CH_2=$CHCH_2$–	62
d	$CH_3CH_2CH_2CH_2CH_2CH_2$–	69
e	*i*-$PrOCH_2CH_2CH_2$–	71
f	$(CH_3)_2CHCH_2$–	70
g	$C_6H_5CH_2CH_2$–	70
h	*t*-C_4H_9	13 [a]
i	$C_6H_5CH_2$–	65
j	*p*-$CH_3OC_6H_4CH_2$–	66
k	*p*-$ClC_6H_4CH_2$–	64
l	*p*-$CF_3C_6H_4CH_2$–	65
m	C_6H_5–	65
n	*p*-$CH_3OC_6H_4$–	74
o	*p*-ClC_6H_4–	66
p	*o*-$CH_3C_6H_4$–	68

[a] This yield was achieved by heating at 180°C for 96 hours

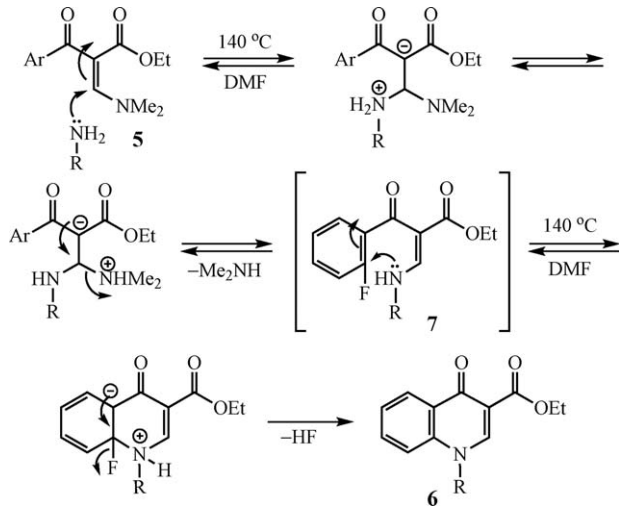
Figure 1. Cyclization of ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylates.

its dianion **3** by reaction with two equivalents of *n*-butyllithium in tetrahydrofuran (THF). Subsequent treatment of **3** with 0.5 equivalents of 2-fluorobenzoyl chloride (**2**) furnished ethyl 2-(2-fluorobenzoyl)acetate (**4**) in 85% yield [10]. Condensation of this β-ketoester with *N*,*N*-dimethylformamide dimethyl acetal in DMF at 100°C for 30 min then afforded β-enaminone substrate **5** in 97% yield [11]. Many of the ^{1}H- and ^{13}C-NMR signals for this compound were very broad, making it difficult to assign *E* and *Z* double bond isomers and determine their ratio. However, because both isomers react to give the target heterocycles, the *E*/*Z* mixture was used as isolated.

The results of our cyclization study are given in Figure 1. Treatment of enaminone **5** with an equimolar quantity of a primary amine (RNH_2) in DMF under argon at 140°C for 48 h afforded the target ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylates **6** in 60–70% yields [12]. Reactions were conveniently run in a Pyrex pressure vessel, though this was only necessary for amines with boiling points less than 100°C (Fig. 1, entries **a**, **c**, **f**, and **h**). The dihydroquinolines derived from most of the amines studied were crystalline and, thus, easily purified by trituration in ether. Products that were not solid were readily purified by preparative thin layer chromatography eluted with ethyl acetate followed by trituration in ether–petroleum ether mixtures.

The reaction was successful for primary amines incorporating cyclic (entries **a–b**), straight-chain (entries **c–g**), benzylic (entries **i–l**), and aromatic (entries **m–p**) R groups. In fact, the target heterocycles were produced in similar yields from all amines used, except when R was a tertiary alkyl group. *tert*-Butylamine (entry **h**) reacted poorly to give <5% of **6h** under our standard conditions (140°C, 48 h) and only 13% under more forcing conditions (180°C, 96 h); a longer reaction time did not significantly improve this yield. Surprisingly, hindered aromatic amines, such as *ortho*-toluidine (entry **p**), afforded the corresponding 1,4-dihydro-4-oxo-3-quinolinecarboxylate **6p** in a respectable 68% yield, despite the steric congestion created by the *ortho* methyl group. Thus, the current method appears to be a general route to these compounds except when R is tertiary.

Scheme 2. Proposed mechanism for the cyclization.



The proposed mechanism of the process is summarized in Scheme 2. The sequence involves an initial conjugate addition of the amine to enaminone **5** followed by elimination of the dimethylamino group to give adduct **7**. If the reaction is performed at 80°C, a significant quantity of this addition-elimination product is isolated from the reaction. At 140°C, however, adduct **7** continues on to give **6** by an S_NAr ring closure reaction. Because the addition process is reversible, *E*- and *Z*-**7** can equilibrate to the *E* adduct required for cyclization.

CONCLUSION

We have developed an alternative synthesis of *N*-substituted ethyl 1,4-dihydro-4-oxo-3-quinolinecarboxylates, which could potentially provide access to new derivatives of these valuable pharmaceutical building blocks. The synthesis is simple and gives the target heterocycles in 60–74% yields, which represents a slight improvement over previous methods. The synthesis appears to be general for all primary amines except those where the R of the primary amine is a tertiary alkyl group.

EXPERIMENTAL

All reactions were run under dry nitrogen or argon in oven-dried glassware. Commercial anhydrous *N,N*-dimethylformamide (DMF) was stored under nitrogen and transferred by syringe into reactions where it was used. Tetrahydrofuran (THF) was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride under nitrogen. Other reagents and solvents were used as received. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech No. 21521). Preparative separations were performed using flash column chromatography [13] on silica gel (Grade 62, 60–200 mesh) mixed with ultraviolet-active phosphor (Sorbent Technologies No. UV-5) or preparative thin layer chromatography on 20-cm × 20-cm silica gel GF plates (Analtech No. 02015); band elution for both methods was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. IR spectra were run as thin films on sodium chloride disks. ^{1}H- and ^{13}C-NMR spectra were measured in deuteriochloroform at 300 and 75 MHz, respectively, and were referenced to internal tetramethylsilane; coupling constants (*J*) are reported in Hz. Low-resolution mass spectra (electron impact/direct probe) were run at 30 eV.

Ethyl 2-(2-fluorobenzoyl)acetate (4). The procedure of Domagala et al. [10] was modified. In a three-necked round-bottomed flask equipped with an efficient magnetic stirrer (2.5 cm or larger stir bar), 4.17 g (31.6 mmol) of ethyl hydrogen malonate (**1**) was dissolved in 200 mL of THF and 10 mg of bipyridyl was added as an internal indicator. The mixture was cooled to −30°C and 16.0 mL of 2.0 *M* *n*-butyllithium (32.0 mmol) was added dropwise over 20 min. The reaction mixture was then warmed to −5°C and another portion of 16.0 mL of 2.0 *M* *n*-butyllithium (32.0 mmol) was added until a red color persisted for 5 min. The mixture was cooled to −78°C, and a solution of 2.85 g (18.0 mmol) of 2-fluorobenzoyl chloride (**2**) in 15 mL of THF was added dropwise over 25 min. [Note: The solution became a thick yellow liquid, and stirring was a problem without an efficient magnetic stirrer]. The solution was kept at −78°C for 30 min and then slowly warmed to −30°C and stirred for 30 min. The reaction mixture was poured into 200 mL of ice cold 1 *M* hydrochloric acid and extracted with dichloromethane (3 × 200 mL). The combined organic extracts were washed with water (1 × 200 mL), 5% aqueous sodium bicarbonate (1 × 150 mL) and 1 *N* aqueous hydrochloric acid (1 × 150 mL). The dichloromethane layer was finally washed with saturated aqueous sodium chloride (1 × 150 mL), dried (magnesium sulfate), and then concentrated under vacuum to give a thick yellow oil. The product was purified by flash chromatography on a 40 × 2.5-cm^2 silica gel column eluted with increasing concentrations of ether in hexane to give 3.21 g (85%) of **4** as colorless oil consisting of a 3:1 mixture of the keto and enol. IR: 1743, 1690, 1629, 1614, 1256 cm^{-1}; ^{1}H-NMR (keto): δ 7.94 (td, 1H, J = 7.9, 2.0), 7.57 (m, 1H), 7.25 (m, 1H), 7.15 (m, 1H), 4.21 (q, 2H, J = 7.1), 3.99 (d, 2H, J = 3.6), 1.26 (t, 3H, J = 7.1); ^{13}C-NMR (keto and enol): δ 190.3, 173.3, 167.3 (d, J = 1.5), 166.3 (d, J = 1.5), 162.1 (d, J = 254.5), 160.7 (d, J = 254.6), 135.4 (d, J = 9.4), 132.3 (d, J = 9.2), 130.9 (d, J = 1.5), 129.1 (d, J = 1.5), 124.6 (d, J = 3.1), 124.2 (d, J = 3.4), 116.6 (d, J = 19.2), 116 (d, J = 18.3), 92.6, 92.4, 61.2, 60.4, 49.9, 49.8, 14.2, 14.0; ms: 210 (M^+). *Anal*. Calcd. for $C_{11}H_{11}FO_3$: C, 62.86; H, 5.24. Found: C, 62.96; H, 5.26.

Ethyl 3-(dimethylamino)-2-(2-fluorobenzoyl)acrylate (5). The procedure of Koskinen and coworkers [11] was modified. A 50-mL single-necked round-bottomed flask, equipped with a reflux condenser and a magnetic stirrer, was charged with 1.05 g (5.00 mmol) of **4** and 5 mL of DMF. The resulting solution was heated to 100°C (oil bath), 0.60 g (0.66 mL, 5.00 mmol) of dimethylformamide dimethyl acetal was added, and heating was continued at 100°C for 30 min. The crude reaction mixture was quenched with ice water, stirred for 5 min and extracted with 50 mL of ether. The aqueous solution was saturated with sodium chloride and extracted with additional ether (2 × 50 mL). The combined ether layers were washed with saturated aqueous sodium chloride, dried (magnesium sulfate), and concentrated under vacuum. Further concentration under high vacuum removed traces of DMF to give 1.28 g (97%) of **5** as a mixture of double bond isomers. This oil was used without further purification. IR: 1688, 1629, 1619, 1587, 1281 cm^{-1}; ^{1}H-NMR: δ 7.76 (s, 1H), 7.60 (br s, 1H), 7.37 (m, 1H), 7.17 (td, 1H, J = 7.7, 1.1), 7.02 (t, 1H, J = 8.2), 3.96 (q, 2H, J = 7.1), 3.27 (br s, 3H), 2.95 (br s, 3H), 0.89 (t, 3H, J = 7.1); ^{13}C-NMR: δ 188.0 (br), 167.8 (br), 160.0 (br d, J = 255.1), 157.5, 131.7 (br), 130.5 (d, J = 12.8), 129.8, 123.7 (d, J = 3.4), 115.3 (d, J = 22.6), 103.1 (br), 59.7, 47.9 (br), 42.8 (br), 13.6.

General procedure for the tandem addition-elimination-S_NAr reaction: ethyl 1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6a). A 15-mL, Pyrex pressure vessel (Chemglass CG-1880-01), equipped with a magnetic stirrer, was charged with 132 mg (0.50 mmol) of **5**, 2.0 mL of anhydrous DMF and 28.5 mg (0.035 mL, 0.50 mmol) of cyclopropylamine. The vessel was purged with argon, the cap was tightened, and the reaction was heated at 140°C for 48 h. After cooling, the crude reaction mixture was poured over 20 g of ice and extracted with 15 mL of ethyl acetate. The aqueous layer was saturated with sodium chloride and extracted with additional ethyl acetate (2 ×15 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried (magnesium sulfate), and concentrated under vacuum to give a light brown solid. Trituration with ether and vacuum filtration then gave 88 mg (68%) of **6a** as a tan solid, mp 164–166°C (lit [14] mp 167–168°C). IR: 1721, 1621, 1611 cm^{-1}; ^{1}H-NMR: δ 8.61 (s, 1H), 8.51 (dd, 1H, J = 8.2, 1.6), 7.93 (d, 1H, J = 8.2), 7.71 (ddd, 1H, J = 8.8, 8.0, 1.6), 7.45 (t, 1H, J = 7.7), 4.40 (q, 2H, J = 7.1), 3.48 (m, 1H), 1.42 (t, 3H, J = 7.1), 1.34 (m, 2H), 1.15 (m, 2H); ^{13}C-NMR: δ 174.6, 166.0, 148.6, 140.5, 132.4, 128.6, 127.6, 125.2, 116.3, 111.0, 60.9, 34.4, 14.4, 8.2; ms: *m/z* 257 (M^+). *Anal*. Calcd. for $C_{15}H_{15}NO_3$: C, 70.04; H, 5.84; N, 5.45. Found: C, 69.99; H, 5.81; N, 5.49.

Ethyl 1-cyclohexyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6b). This compound (90 mg, 60%) was prepared from 132 mg (0.50 mmol) of **5** and 49.5 mg (0.057 mL, 0.50 mmol) of cyclohexylamine. The product was isolated as a light yellow oil following preparative thin layer chromatography eluted with ethyl acetate. IR: 1725, 1686, 1630, 1608 cm^{-1}; ^{1}H-NMR: δ 8.70 (s, 1H), 8.58 (dd, 1H, J = 7.7, 1.1), 7.70 (ddd, 1H, J = 8.8, 7.7, 1.6), 7.57 (d, 1H, J = 8.8), 7.44 (td, 1H, J = 7.7, 1.1), 4.45 (obscured m, 1H), 4.41 (q, 2H, J = 7.1), 2.19 (apparent d, 2H, J = 11.0), 2.06 (apparent d, 2H, J = 13.1), 2.00–1.70 (complex, 3H), 1.55 (m, 2H), 1.43 (t, 3H, J = 7.1), 1.36 (obscured m, 1H); ^{13}C-NMR: δ 173.9,

166.3, 144.5, 139.2, 132.4, 129.4, 128.2, 124.8, 114.8, 110.7, 60.8, 59.3, 32.7, 25.8, 25.2, 14.4; ms: *m/z* 299 (M^+). *Anal*. Calcd. for $C_{18}H_{21}NO_3$: C, 72.24; H, 7.02; N, 4.68. Found: C, 72.27; H, 7.06; N, 4.61.

Ethyl 1,4-dihydro-4-oxo-1-(2-propenyl)-3-quinolinecarboxylate (6c). This compound (80 mg, 62%) was prepared from 132 mg (0.50 mmol) of **5** and 28.5 mg (0.038 mL, 0.50 mmol) of allylamine. The product was isolated as a light yellow solid following preparative thin layer chromatography eluted with ethyl acetate, mp 101–103°C (lit [5] mp 98–100°C). IR: 1722, 1690, 1619, 1610 cm^{-1}; ^{1}H-NMR: δ 8.53 (dd, 1H, *J* = 8.2, 1.6), 8.47 (s, 1H), 7.63 (ddd, 1H, *J* = 8.8, 8.0, 1.6), 7.42 (t, 1H, *J* = 7.1), 7.40 (d, 1H, *J* = 7.7), 6.02 (ddt, 1H, *J* = 17.0, 10.4, 4.9), 5.36 (d, 1H, *J* = 10.4), 5.20 (d, 1H, *J* = 17.0), 4.81 (d, 2H, *J* = 4.9), 4.40 (q, 2H, *J* = 7.1), 1.42 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 174.3, 165.7, 149.1, 139.0, 132.4, 130.5, 129.0, 127.8, 125.0, 119.3, 116.1, 111.1, 60.8, 55.6, 14.4; ms: *m/z* 257 (M^+). *Anal*. Calcd. for $C_{15}H_{15}NO_3$: C, 70.04; H, 5.84; N, 5.45. Found: C, 70.06; H, 5.85; N, 5.42.

Ethyl 1-hexyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6d). This compound (104 mg, 69%) was prepared from 132 mg (0.50 mmol) of **5** and 50.5 mg (0.066 mL, 0.50 mmol) of hexylamine. The product was isolated as a white solid following workup and trituration with 1:2 ether:petroleum ether, mp 79–80°C. IR: 1727, 1691, 1632, 1609 cm^{-1}; ^{1}H-NMR: δ 8.54 (dd, 1H, *J* = 8.2, 1.1), 8.47 (s, 1H), 7.68 (ddd, 1H, *J* = 8.2, 7.4, 1.6), 7.44 (d, 1H, *J* = 7.7), 7.43 (obscured t, 1H, *J* = 7.1), 4.41 (q, 2H, *J* = 7.1), 4.18 (t, 2H, *J* = 7.1), 1.89 (quintet, 2H, *J* = 7.1), 1.42 (t, 3H, *J* = 7.1), 1.34 (m, 6H), 0.89 (distorted t, 3H, *J* = 7.1); ^{13}C-NMR: δ 174.2, 165.9, 149.0, 138.7, 132.4, 129.3, 128.0, 124.9, 115.6, 110.7, 60.8, 54.0, 31.2, 28.8, 26.2, 22.4, 14.4, 13.8; ms: *m/z* 230 (M^+-C_5H_{11}). *Anal*. Calcd. for $C_{18}H_{23}NO_3$: C, 71.76; H, 7.64; N, 4.65. Found: C, 71.79; H, 7.67; N, 4.59.

Ethyl 1,4-dihydro-1-(3-isopropoxypropyl)-4-oxo-3-quinolinecarboxylate (6e). This compound (110 mg, 69%) was prepared from 132 mg (0.50 mmol) of **5** and 58.5 mg (0.069 mL, 0.50 mmol) of 3-isopropoxypropylamine. The product was isolated as a light yellow solid following preparative thin layer chromatography eluted with ethyl acetate, mp 64–66°C. IR: 1726, 1692, 1631, 1613 cm^{-1}; ^{1}H-NMR: δ 8.54 (obscured dd, 1H, *J* = 7.7, 1.6), 8.53 (s, 1H), 7.68 (ddd, 1H, *J* = 8.2, 7.7, 1.6), 7.53 (d, 1H, *J* = 8.2), 7.42 (td, 1H, *J* = 7.7, 1.1), 4.41 (t, 2H, *J* = 7.1, 4.37 (q, 2H, *J* = 7.1), 3.55 (septet, 1H, *J* = 6.0), 3.38 (t, 2H, *J* = 5.5), 2.12 (quintet, 2H, *J* = 5.5), 1.41 (t, 3H, *J* = 7.1), 1.19 (d, 6H, *J* = 6.0); ^{13}C-NMR: δ 174.4, 165.6, 149.7, 138.7, 132.4, 129.2, 128.0, 124.9, 115.7, 110.5, 71.9, 63.1, 60.7, 50.5, 28.7, 21.9, 14.4; ms: *m/z* 230 (M^+-$C_5H_{11}O$). *Anal*. Calcd. for $C_{18}H_{23}NO_4$: C, 68.14; H, 7.26; N, 4.42. Found: C, 68.18; H, 7.29; N, 4.36.

Ethyl 1,4-dihydro-1-isobutyl-4-oxo-3-quinolinecarboxylate (6f). This compound (95 mg, 70%) was prepared from 132 mg (0.50 mmol) of **5** and 36.5 mg (0.050 mL, 0.50 mmol) of isobutylamine. The product was isolated as a light yellow solid following preparative thin layer chromatography eluted with ethyl acetate, mp 90–91°C. IR: 1724, 1689, 1626, 1610 cm^{-1}; ^{1}H-NMR: δ 8.54 (dd, 1H, *J* = 8.2, 1.6), 8.43 (s, 1H), 7.68 (ddd, 1H, *J* = 8.8, 7.9, 1.6), 7.43 (d, 1H, *J* = 8.8), 7.43 (t, 1H, *J* = 7.1), 4.40 (q, 2H, *J* = 7.1), 3.99 (d, 2H, *J* = 7.7), 2.29 (nonet, 1H, *J* = 7.1), 1.42 (t, 3H, *J* = 7.1), 1.01 (d, 6H, *J* = 6.8); ^{13}C-NMR: δ 174.2, 165.9, 149.4, 138.8, 132.3, 129.1, 127.9, 124.9, 115.8, 110.3, 61.2, 60.7, 27.5, 20.0 (2C), 14.3; ms: *m/z* 230 (M^+-C_3H_7). *Anal*. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.41; H, 7.01; N, 5.05.

Ethyl 1,4-dihydro-4-oxo-1-(2-phenylethyl)-3-quinolinecarboxylate (6g). This compound (112 mg, 70%) was prepared from 132 mg (0.50 mmol) of **5** and 60.5 mg (0.063 mL, 0.50 mmol) of 2-phenylethylamine. The product was isolated as a light yellow oil following preparative thin layer chromatography eluted with ethyl acetate. IR: 1723, 1690, 1628, 1611 cm^{-1}; ^{1}H-NMR: δ 8.55 (dd, 1H, *J* = 8.2, 1.6), 8.13 (s, 1H), 7.71 (ddd, 1H, *J* = 8.2, 7.4, 1.6), 7.51 (d, 1H, *J* = 8.8), 7.44 (t, 1H), *J* = 7.4), 7.28 (m, 4H), 7.08 (dd, 1H, *J* = 7.7, 1.6), 4.40 (t, 2H, *J* = 7.1), 4.32 (q, 2H, *J* = 7.1), 3.16 (t, 2H, *J* = 7.1), 1.35 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 174.2, 165.4, 149.0, 138.5, 136.3, 132.6, 129.1, 129.0, 128.6, 128.1, 127.4, 125.0, 115.4, 110.5, 60.6, 55.1, 35.0, 14.3; ms: *m/z* 230 (M^+-C_7H_7). *Anal*. Calcd. for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.81; H, 5.90; N, 4.31.

Ethyl 1-*tert*-butyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6h). This compound (18 mg, 13%) was prepared from 132 mg (0.5 mmol) of **5** and 36.5 mg (0.054 mL, 0.50 mmol) of *tert*-butylamine. This reaction was unique in requiring a higher temperature and a longer reaction time (180°C, 96 h). The product was isolated as a light yellow solid following preparative thin layer chromatography eluted with ethyl acetate, mp 172–174°C. IR: 1728, 1687, 1638, 1602 cm^{-1}; ^{1}H-NMR: δ 8.93 (s, 1H), 8.64 (dd, 1H, *J* = 8.2, 1.6), 7.93 (d, 1H, *J* = 8.8), 7.65 (ddd, 1H, *J* = 8.8, 7.1, 1.6), 7.43 (t, 1H, *J* = 7.1), 4.41 (q, 2H, *J* = 7.1), 1.89 (s, 9H), 1.43 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 173.9, 166.7, 146.1, 138.9, 130.9, 130.7, 128.5, 124.6, 119.7, 109.8, 63.0, 60.9, 30.7 (3C), 14.4; ms: *m/z* 258 (M^+-CH_3). *Anal*. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.36; H, 6.97; N, 5.10.

Ethyl 1-benzyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6i). This compound (100 mg, 65%) was prepared from 132 mg (0.50 mmol) of **5** and 53.5 mg (0.055 mL, 0.50 mmol) of benzylamine. The product was isolated as a tan solid following workup and trituration with ether, mp 168–170°C (lit [4] mp 120–121°C). IR: 1724, 1690, 1629, 1614 cm^{-1}; ^{1}H-NMR: δ 8.60 (s, 1H), 8.53 (dd, 1H, *J* = 8.2, 1.6), 7.54 (ddd, 1H, *J* = 8.8, 7.1, 1.6), 7.42–7.28 (complex, 6H), 7.17 (dd, 1H, *J* = 7.7, 1.6), 5.41 (s, 2H), 4.40 (q, 2H, *J* = 7.1), 1.41 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 174.3, 165.7, 149.7, 139.1, 134.2, 132.5, 129.3, 129.2, 128.5, 127.8, 126.0, 125.1, 116.5, 111.1, 60.9, 57.3, 14.4; ms: *m/z* 307 (M^+). *Anal*. Calcd. for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.31; H, 5.55; N, 4.52.

Ethyl 1,4-dihydro-1-(4-methoxybenzyl)-4-oxo-3-quinolinecarboxylate (6j). This compound (111 mg, 66%) was prepared from 132 mg (0.50 mmol) of **5** and 68.5 mg (0.065 mL, 0.50 mmol) of 4-methoxybenzylamine. The product was isolated as a tan solid following workup and trituration with ether, mp 124–125°C. IR: 2838, 1723, 1689, 1621, 1611 cm^{-1}; ^{1}H-NMR δ 8.60 (s, 1H), 8.53 (dd, 1H, *J* = 7.7, 1.1), 7.56 (ddd, 1H, *J* = 8.2, 7.7, 1.1), 7.38 (m, 2H), 7.12 (d, 2H, *J* = 8.8), 6.88 (d, 2H, *J* = 8.8), 5.34 (s, 2H), 4.41 (q, 2H, *J* = 7.1), 3.78 (s, 3H), 1.42 (t, 3H, *J* = 7.1); ^{13}C-NMR: δ 174.4, 165.9, 159.7, 149.5, 139.1, 132.5, 129.3, 127.9, 127.6, 126.0, 125.1, 116.5, 114.7, 111.1, 60.9, 56.9, 55.3, 14.4; ms: *m/z* 337 (M^+). *Anal*. Calcd. for $C_{20}H_{19}NO_4$: C, 71.22; H, 5.64; N, 4.15. Found: C, 71.17; H, 5.65; N, 4.09.

Ethyl 1-(4-chlorobenzyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6k). This compound (109 mg, 64%) was prepared from 132 mg (0.50 mmol) of **5** and 70.8 mg (0.061 mL,

0.50 mmol) of 4-chlorobenzylamine. The product was isolated as a tan solid following workup and trituration with ether, mp 208–210°C (lit [15] mp 145–146°C). IR: 1722, 1688, 1621, 1611 cm^{-1}; ^{1}H-NMR: δ 8.60 (s, 1H), 8.54 (dd, 1H, J = 7.7, 1.1), 7.56 (ddd, 1H, J = 8.2, 7.7, 1.1), 7.41 (t, 1H, J = 7.1), 7.34 (d, 2H, J = 8.2), 7.26 (d, 1H, J = 8.2), 7.11 (d, 2H, J = 8.2), 5.38 (s, 2H), 4.42 (q, 2H, J = 7.1), 1.42 (t, 3H, J = 7.1); ^{13}C-NMR: δ 174.8, 165.8, 149.6, 138.9, 134.6, 132.8, 132.7, 129.6, 129.3, 128.1, 127.4, 125.3, 116.3, 111.5, 61.0, 56.7, 14.4; ms: *m*/*z* 341, 343 (*ca* 3:1, M^+). *Anal*. Calcd. for $C_{19}H_{16}ClNO_3$: C, 66.76; H, 4.69; N, 4.10. Found: C, 66.81; H, 4.72; N, 4.03.

Ethyl 1,4-dihydro-4-oxo-1-(4-trifluoromethylbenzyl)-3-quinolinecarboxylate (6l). This compound (122 mg, 65%) was prepared from 132 mg (0.50 mmol) of **5** and 87.5 mg (0.071 mL, 0.50 mmol) of 4-(trifluoromethyl)benzylamine. The product was isolated as a tan solid following workup and trituration with ether, mp 246–248°C. IR: 1722, 1678, 1642, 1611 cm^{-1}; ^{1}H-NMR: δ 8.61 (s, 1H), 8.56 (d, 1H, J = 7.7), 7.64 (d, 2H, J = 7.7), 7.56 (t, 1H, J = 7.4), 7.42 (t, 1H, J = 7.4), 7.29 (d, 2H, J = 7.7), 7.22 (d, 1H, J = 7.7), 5.47 (s, 2H), 4.42 (q, 2H, J = 7.1), 1.43 (t, 3H, J = 7.1); ^{13}C-NMR [16]: δ 174.3, 165.7, 149.6, 138.9, 138.4, 132.8, 131.0 (q, J = 33.2), 129.3, 128.2, 126.4 (q, J = 3.7), 126.3, 125.4, 123.6 (q, J = 271.6), 116.1, 111.7, 61.1, 56.8, 14.4; ms: *m*/*z* 375 (M^+). *Anal*. Calcd. for $C_{20}H_{16}F_3NO_3$: C, 64.00; H, 4.27; N, 3.73. Found: C, 64.11; H, 4.29; N, 3.68. On storage, this compound converts to a highly insoluble unidentified material.

Ethyl 1,4-dihydro-4-oxo-1-phenyl-3-quinolinecarboxylate (6m). This compound (95 mg, 65%) was prepared from 132 mg (0.50 mmol) of **5** and 46.5 mg (0.045 mL, 0.50 mmol) of aniline. The product was isolated as a tan solid following workup and trituration with ether, mp 208–209°C. IR: 1726, 1690, 1623, 1608 cm^{-1}; ^{1}H-NMR: δ 8.56 (dd, 1H, J = 7.7, 1.6), 8.53 (s, 1H), 7.67–7.60 (complex, 3H), 7.52 (ddd, 1H, J = 8.8, 7.1, 1.6), 7.43 (complex, 3H), 6.99 (d, 1H, J = 8.2), 4.40 (q, 2H, J = 7.1), 1.41 (t, 3H, J = 7.1); ^{13}C-NMR: δ 174.4, 165.7, 148.7, 140.7, 135.7, 132.3, 130.4, 130.0, 128.4, 127.5, 127.4, 125.2, 117.6, 111.4, 60.9, 14.4; ms: *m*/*z* 293 (M^+). *Anal*. Calcd. for $C_{18}H_{15}NO_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.68; H, 5.13; N, 4.74.

Ethyl 1,4-dihydro-1-(4-methoxyphenyl)-4-oxo-3-quinolinecarboxylate (6n). This compound (119 mg, 74%) was prepared from 132 mg (0.50 mmol) of **5** and 61.5 mg (0.50 mmol) of 4-methoxyaniline. The product was isolated as a light yellow solid following workup and trituration with ether, mp 202–204°C. IR: 2840, 1728, 1690, 1633, 1611 cm^{-1}; ^{1}H-NMR: δ 8.55 (dd, 1H, J = 7.7, 1.6), 8.51 (s, 1H), 7.52 (ddd, 1H, J = 8.8, 7.1, 1.6), 7.42 (td, 1H, J = 7.7, 1.1), 7.34 (d, 2H, J = 8.8), 7.10 (d, 2H, J = 8.8), 6.99 (d, 1H, J = 8.8), 4.39 (q, 2H, J = 7.1), 3.92 (s, 3H), 1.40 (t, 3H, J = 7.1); ^{13}C-NMR: δ 174.4, 165.7, 160.4, 149.0, 141.0, 133.3, 132.2, 128.5, 128.4, 127.4, 125.1, 117.7, 115.4, 111.2, 60.9, 55.7, 14.4; ms: *m*/*z* 323 (M^+). *Anal*. Calcd. for $C_{19}H_{17}NO_4$: C, 70.59; H, 5.26; N, 4.33. Found: 70.66; H, 5.29; N, 4.28.

Ethyl 1-(4-chlorophenyl)-1,4-dihydro-4-oxo-3-quinolinecarboxylate (6o). This compound (108 mg, 66%) was prepared from 132 mg (0.50 mmol) of **5** and 64.0 mg (0.50 mmol) of 4-chloroaniline. The product was isolated as a light yellow solid following workup and trituration with ether, mp 186–188°C. IR: 1728, 1693, 1633, 1610 cm^{-1}; ^{1}H-NMR: δ 8.54 (dd, 1H, J = 7.7, 1.6), 8.47 (s, 1H), 7.62 (d, 2H, J = 8.8), 7.54 (ddd, 1H, J = 8.8, 7.1, 1.6), 7.43 (td, 1H, J = 7.7, 1.1), 7.41 (d, 2H, J = 8.8), 6.97 (d, 1H, J = 8.8), 4.39 (q, 2H, J = 7.1), 1.40 (t, 3H, J = 7.1); ^{13}C-NMR: δ 174.3, 165.4, 148.4, 140.4, 139.1, 136.2, 132.4, 130.7, 128.8, 128.3, 127.6, 125.4, 117.3, 111.6, 61.0, 14.4; ms: *m*/*z* 327, 329 (*ca* 3:1, M^+). *Anal*. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.95; H, 4.27; N, 4.27. Found: C, 66.01; H, 4.30; N, 4.19.

Ethyl 1,4-dihydro-1-(2-methylphenyl)-4-oxo-3-quinolinecarboxylate (6p). This compound (104 mg, 68%) was prepared from 132 mg (0.50 mmol) of **5** and 53.5 mg (0.054 mL, 0.50 mmol) of 2-methylaniline. The product was isolated as a light yellow solid following workup and trituration with ether, mp 182–184°C. IR: 1729, 1691, 1634, 1610 cm^{-1}; ^{1}H-NMR: δ 8.57 (dd, 1H, J = 7.7, 1.6), 8.44 (s, 1H), 7.55–7.40 (complex, 5H), 7.33 (d, 1H, J = 7.7), 6.78 (d, 1H, J = 7.7), 4.40 (q, 2H, J = 7.1), 2.07 (s, 3H), 1.41 (t, 3H, J = 7.1); ^{13}C-NMR: δ 174.4, 165.6, 148.4, 140.2, 139.3, 135.7, 132.5, 131.9, 130.3, 128.4, 128.0, 127.9, 127.5, 125.2, 117.1, 111.5, 60.9, 17.1, 14.4; ms: *m*/*z* 307 (M^+). *Anal*. Calcd. for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.31; H, 5.55; N, 4.52.

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