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An economical synthesis of substituted quinoline-2-carboxylates through the potassium persulfate-mediated cross-dehydrogenative coupling of *N*-aryl glycine derivatives with olefins†

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A practical and economical $K_2S_2O_8$-mediated oxidative cross-dehydrogenative coupling of *N*-aryl glycine derivatives with olefins has been established, affording structurally diverse quinoline-2-carboxylates in good to high efficiency. The low cost, negligible toxicity, and ease of handling of $K_2S_2O_8$ combined with the absence of hazardous byproducts and the easy workup consisting of simple filtration are attractive based on economic and environmental factors.

Introduction

Quinoline-2-carboxylate (Q2C) derivatives are present in a number of biologically active natural products and synthetic pharmaceuticals possessing diverse activities including antibacterial, anticancer, anti-HIV, anti-inflammatory, and anti-tuberculosis activities.[1,2] For example, Q2C **A** is an inhibitor against the vesicular glutamate transport (VGLUT) protein (Fig. 1).[2a] Q2C **B** is a potent 5-hydroxytryptamine antagonist.[1e] Q2C **C** is a potent lead compound for inhibiting the binding of Insulin-like Growth Factor (IGF) to IGF-binding proteins.[1f] Besides their importance in life sciences, Q2C derivatives can also act as functional molecules in other research fields.[3] For instance, Q2C **D** was found to be a promising biocompatible fluorescent tag.[3b] The simple Q2C **E** is the real intermediate for the synthesis of quinox ligands which have been widely employed in asymmetric catalysis.[3c]

Due to the importance of Q2Cs in modern pharmacology and organic synthesis, significant efforts have been devoted to their synthesis.[4] Recently, the direct cross-dehydrogenative coupling (CDC) of readily accessible substrates has emerged as an effective alternative to conventional protocols for the synthesis of complex molecules.[5] The CDC reactions involving α-amino acid derivatives as substrates have received considerable attention.[6] In 2011, the Mancheño group developed an elegant method to prepare substituted Q2C derivatives through CDC of *N*-aryl glycine esters with styrenes mediated by $FeCl_3$ and TEMPO oxoammonium salt ($T^+BF_4^-$).[7] Jia and Wang disclosed that the same reaction can be promoted in the presence of catalytic $InCl_3$ and tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\bullet}$) employing molecular oxygen as the terminal oxidant.[8] Both systems afforded substituted Q2Cs in high efficiency. However, the oxidation systems are still not ideal from an economic viewpoint. $T^+BF_4^-$ is not commercially available, and the preparation requires extra effort. In the latter case, while molecular oxygen is an ideal terminal oxidant, $TBPA^{+\bullet}$, the precursor of the real oxidant, is rather expensive, with a cost of $9226 per mol according to 2014–2015 Aldrich catalog even if

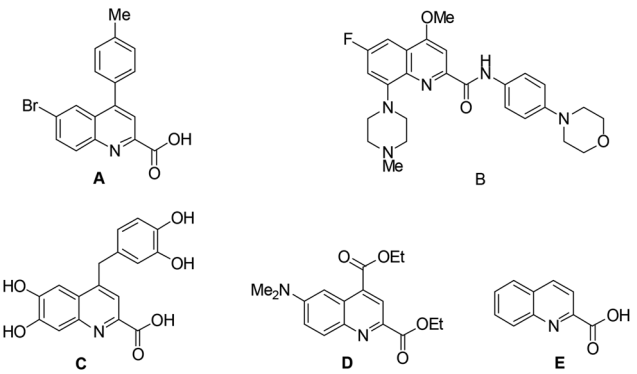

Fig. 1 Representative Q2C derivatives.

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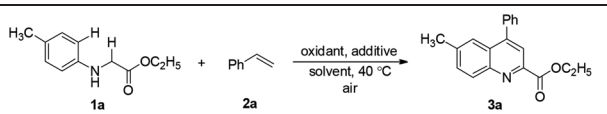
only 10 mol% of $TBPA^{+\bullet}$ is employed. In 2014, Huo reported an elegant auto-oxidative coupling system to prepare the Q2C derivatives using air as the sole oxidant.[9] However, only moderate reaction efficiency was obtained. Such issues led to a search for an economical and efficient oxidation system for the CDC reaction affording substituted Q2C derivatives.

Persulfate has long been known to oxidize hydrocarbons initiated by a single electron transfer process.[10,11] The oxidant is inexpensive, less toxic, and easily handled. The price of persulfates like $K_2S_2O_8$ is only $39 per mol according to 2014–2015 Aldrich catalog, and the byproduct can be easily removed with a simple filtration over Celite or by washing with H_2O.[10] Therefore, the synthesis of substituted Q2Cs through the persulfate mediated CDC of glycine derivatives with olefins would be attractive based on economic and environmental factors.[12]

Results and discussion

Initially, the CDC of glycine ester **1a** with styrene (**2a**) was chosen as a model reaction for optimization (Table 1). When 1 equiv. of $Na_2S_2O_8$ was employed as the oxidant, the desired quinoline **3a** was observed in 9% yield (entry 1, Table 1).

Table 1 Reaction condition optimization[a]



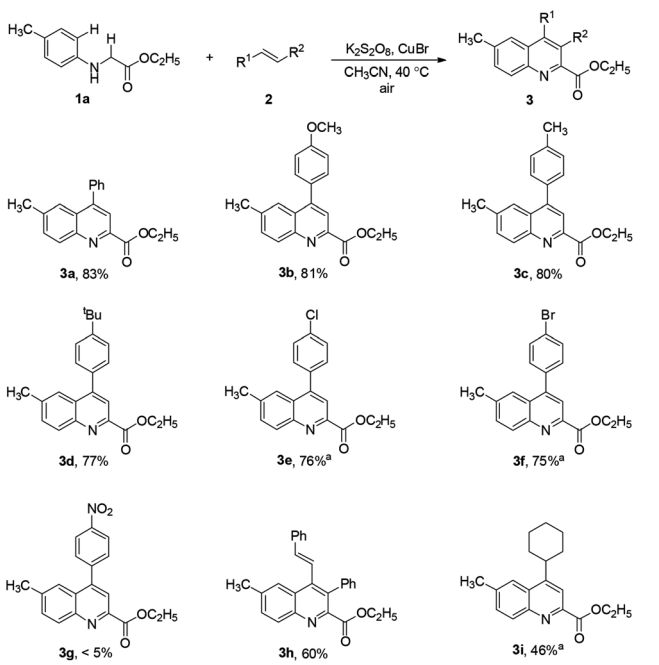
1a 2a 3a

Entry	Oxidant (1.0 equiv.)	Additive (10 mol%)	Solvent	Yield[b] (%)
1	$Na_2S_2O_8$	—	$ClCH_2CH_2Cl$	9
2	$Na_2S_2O_8$	$CuBr_2$	$ClCH_2CH_2Cl$	43
3	$Na_2S_2O_8$	$Cu_3(PO_4)_2$	$ClCH_2CH_2Cl$	25
4	$Na_2S_2O_8$	$Cu(OTf)_2$	$ClCH_2CH_2Cl$	31
5	$Na_2S_2O_8$	CuOAc	$ClCH_2CH_2Cl$	<5
6	$Na_2S_2O_8$	$CuOTf{\cdot}C_6H_6$	$ClCH_2CH_2Cl$	16
7	$Na_2S_2O_8$	$Cu(MeCN)_4PF_6$	$ClCH_2CH_2Cl$	40
8	$Na_2S_2O_8$	CuCl	$ClCH_2CH_2Cl$	58
9	$Na_2S_2O_8$	CuBr	$ClCH_2CH_2Cl$	67
10	$Na_2S_2O_8$	LiOTf	$ClCH_2CHCl$	30
11	$Na_2S_2O_8$	$Mg(OTf)_2$	$ClCH_2CH_2Cl$	<5
12	$Na_2S_2O_8$	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	<5
13	$Na_2S_2O_8$	$FeCl_3$	$ClCH_2CH_2Cl$	26
14	$Na_2S_2O_8$	$FeCl_2$	$ClCH_2CH_2Cl$	20
15	$Na_2S_2O_8$	CuBr	CH_2Cl_2	41
16	$Na_2S_2O_8$	CuBr	CH_3CN	80
17	$Na_2S_2O_8$	CuBr	THF	57
18	$Na_2S_2O_8$	CuBr	Toluene	33
19	$Na_2S_2O_8$	CuBr	EtOAc	46
20	$K_2S_2O_8$	CuBr	CH_3CN	83
21	$(NH_4)_2S_2O_8$	CuBr	CH_3CN	62
22[c]	$K_2S_2O_8$	CuBr	CH_3CN	78
23[d]	$K_2S_2O_8$	CuBr	CH_3CN	62
24[e]	$K_2S_2O_8$	CuBr	CH_3CN	80

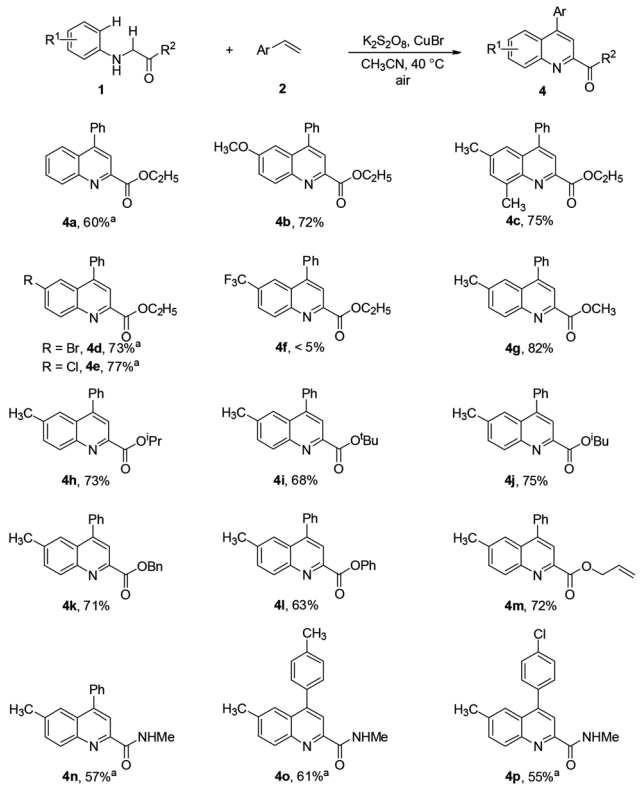
[a] General conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), oxidant (0.1 mmol), additive (0.01 mmol), solvent (1.0 mL) under air at 40 °C for 16 h, unless stated otherwise. [b] Isolated yield. [c] Reaction at 60 °C. [d] Reaction at room temperature. [e] Reaction under Ar.

A variety of different metal salt additives (10 mol%) were explored to improve the reaction efficiency (entries 2–14, Table 1). While several additives including CuOAc, $Mg(OTf)_2$, and $Yb(OTf)_3$ inhibited the reaction, other salts like $CuBr_2$, CuCl, CuBr, and LiOTf[13] proved to be beneficial for improving the efficiency, with CuBr affording the best yields (entry 9, Table 1). The reaction was found to be highly dependent on the solvent choice, and CH_3CN was identified as the optimal candidate (entries 9 and 15–19). Other types of persulfates including $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were next investigated, and the former proved to be the best oxidant (entries 16, 20 and 21). Either elevating or lowering the reaction temperature resulted in inferior yields (entries 20, 22 and 23). Reaction under an Ar atmosphere resulted in a slight loss of the efficiency (entries 20 and 24, Table 1).

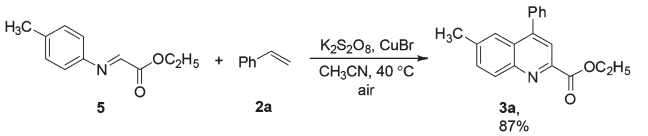
With the optimized reaction conditions in hand, the scope of olefin components was first examined (Scheme 1). A wide range of electronically varied styrenes with different substitution patterns participated in the oxidative CDC reactions with glycine ester **1a**, affording diverse Q2C derivatives **3a–3f** in good to high efficiency (Scheme 1). The reaction efficiency was found to be not sensitive to the electronic substituent effect on the aryl rings except for the styrene bearing strong electron-withdrawing substituent like **2g**. Bromo and chloro substituents were compatible with the oxidation system, which will be beneficial for further diversification. 1,2-Disubstituted olefin **2h** was also a competent component, providing 2,3,4-trisubstituted Q2C **3h** in excellent regioselectivity with an alkene installed at the 4-position for further manipulation. Aliphatic olefin **2i** also participated in the CDC reaction, albeit moderate yield (46%) was obtained.



Scheme 1 The scope of olefin components. [a]Reaction at 60 °C.



Scheme 2 The scope of *N*-aryl glycine derivatives. [a]Reaction at 60 °C.



Scheme 3 The mechanistic study.

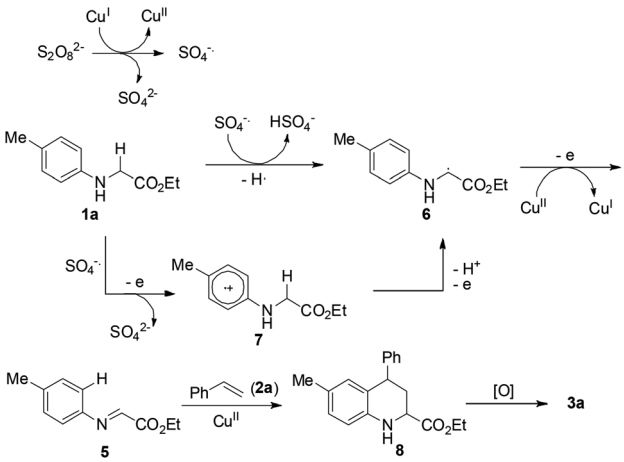


Fig. 2 A proposed mechanism for the oxidative CDC reaction.

The scope of glycine derivatives was next investigated (Scheme 2). The electronic substituent effect on the aniline fragment was first studied. A variety of anilines **1** bearing electron-donating and -withdrawing substituents joined in the CDC reaction with **2a** smoothly afforded the corresponding Q2C products **4a–4e** in good yields (Scheme 2). No reaction was observed for aniline **1f** bearing a strong electron-withdrawing CF_3 moiety. The carboxylic fragment was next explored. Besides the ethyl ester **1a**, other commonly encountered alkyl esters including methyl **1g**, isopropyl **1h**, *tert*-butyl **1i**, isobutyl **1j**, benzyl **1k**, and allyl moieties **1m** as well as aryl ester **1l** also proved to be suitable components for the oxidative CDC reaction with **2a**, affording Q2C **4g–4m** in good yields. *N*-Phenylglycine amides were also tolerated in the economical oxidation system (**4n–4p**).

While the mechanism is not yet fully understood, radical intermediates should be involved in the reaction since 1 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl free radical) completely blocked the transformation. During the course of the reaction of **1a** with **2a**, a considerable amount of an intermediate was detected by TLC analysis, which was identified as imine **5**. Therefore, a control experiment was conducted by subjecting **5** to the standard reaction conditions (Scheme 3). The reaction gave a comparable result to that starting from **1a**, indicating that **5** might be involved in the reaction.

A tentative mechanism for the CDC reaction of glycine ester (**1a**) with styrene (**2a**) is proposed in Fig. 2. We envisioned that the *N*-aryl imine **5** might be the intermediate for the subsequent nucleophilic addition process by **2a** and the final aromatization step.[14] According to the literature, Cu(I) could promote the decomposition of the persulfate to generate the SO_4 radical anion together with the formation of Cu(II) under thermal conditions.[10,11] Two pathways have been postulated for the generation of the imine **5** from **1a**. The first pathway proceeds through an initial hydrogen atom abstraction from **1a** to the SO_4 radical anion giving free radical **6**, which then undergoes one electron oxidation by Cu(II) to afford intermediate **5**. Alternatively, an initial electron transfer from **1a** to the SO_4 radical anion provides the radical cation **7**, which then proceeds through a proton abstraction followed by a second electron transfer to generate intermediate **5**. In the presence of Cu(II), **5** reacts with styrene **2a** to afford intermediate **8** that was further oxidized and aromatized to quinoline **3a**.

Conclusions

In summary, a practical and economical $K_2S_2O_8$-mediated oxidation system for the CDC reaction of a variety of *N*-aryl glycine derivatives with olefins has been established, affording structurally diverse Q2Cs in good to high efficiency. The low cost, negligible toxicity, and ease of handling of $K_2S_2O_8$ combined with the absence of hazardous byproducts and the easy workup consisting of simple filtration are attractive.

Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300, 400, or 600 MHz and 75, 100, or 151 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23 ppm. Analytical TLC was performed on precoated silica gel GF254 plates. HRMS was carried out on an Orbitrap analyzer.

General procedure for the CDC reaction

In a 10 mL sealed tube, to the solution of **1a** (0.1 mmol, 1.0 equiv.) and **2a** (0.2 mmol, 2.0 equiv.) in CH_3CN (1.0 mL) were added CuBr (0.01 mmol, 10 mol%) and $K_2S_2O_8$ (0.1 mmol, 1.0 equiv.). The resulting solution was stirred at 40 °C for 16–24 h, before the reaction mixture was filtered through a Celite pad. The mixture was evaporated under vacuum and the residue was purified by flash chromatography using ethyl acetate/petroleum ether (10 : 90) as the eluent to afford **3a**.

Characterization data for the products in Scheme 1

Ethyl 6-methyl-4-phenylquinoline-2-carboxylate (3a). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.63 (dd, J = 8.7, 1.8 Hz, 1H), 7.60–7.47 (m, 5H), 4.57 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H). These data are consistent with the reported literature values.[8]

Ethyl 4-(4-methoxyphenyl)-6-methylquinoline-2-carboxylate (3b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.7 Hz, 1H), 8.08 (s, 1H), 7.76 (s, 1H), 7.66–7.55 (m, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 4.57 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.51 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H). These data are consistent with the reported literature values.[8]

Ethyl 6-methyl-4-*p*-tolylquinoline-2-carboxylate (3c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 1H), 8.09 (s, 1H), 7.74 (s, 1H), 7.67–7.58 (m, 1H), 7.49–7.33 (m, 4H), 4.56 (q, J = 7.1 Hz, 2H), 2.58–2.43 (m, 6H), 1.49 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 4-(4-*tert*-butylphenyl)-6-methylquinoline-2-carboxylate (3d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H), 7.79 (s, 1H), 7.68–7.55 (m, 3H), 7.55–7.42 (m, 2H), 4.56 (q, J = 7.1 Hz, 2H), 2.52 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H). The data are consistent with the known literature.[8]

Ethyl 4-(4-chlorophenyl)-6-methylquinoline-2-carboxylate (3e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9.2 Hz, 1H), 8.07 (s, 1H), 7.64 (d, J = 6.9 Hz, 2H), 7.60–7.42 (m, 4H), 4.57 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 4-(4-bromophenyl)-6-methylquinoline-2-carboxylate (3f). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9.2 Hz, 1H), 8.07 (s, 1H), 7.78–7.59 (m, 4H), 7.47–7.35 (m, 2H), 4.57 (q, J = 7.1 Hz, 2H), 2.51 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.8, 147.2, 147.1, 139.5, 136.9, 132.7, 132.1, 131.4, 131.3, 127.7, 124.5, 123.3, 121.5, 62.5, 22.3, 14.6; IR ν_{max} 2921, 2851, 1711, 1593, 1488, 1378, 1250, 1205, 1148, 1109, 1010, 848, 822, 790 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{16}BrNO_2$ $[M + H]^+$ 370.0437, found 370.0445.

(*E*)-Ethyl 6-methyl-3-phenyl-4-styrylquinoline-2-carboxylate (3h). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 1H), 8.07 (s, 1H), 7.62 (dd, J = 8.6, 1.8 Hz, 1H), 7.50–7.28 (m, 10H), 7.08 (d, J = 16.7 Hz, 1H), 6.78 (d, J = 16.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 4-cyclohexyl-6-methylquinoline-2-carboxylate (3i). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 1H), 8.06 (s, 1H), 7.86 (s, 1H), 7.58 (dd, J = 8.7, 1.7 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 3.42–3.27 (m, 1H), 2.60 (s, 3H), 2.07–1.83 (m, 5H), 1.72–1.54 (m, 5H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 154.2, 147.4, 146.7, 138.4, 131.9, 131.6, 128.1, 121.9, 117.7, 62.2, 39.2, 33.6, 27.0, 26.4, 22.4, 14.6; IR ν_{max} 3061, 2923, 2851, 1715, 1583, 1506, 1446, 1369, 1342, 1264, 1211, 1146, 1024, 946, 899, 825, 793 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{23}NO_2$ $[M + H]^+$ 298.1802, found 298.1803.

Characterization data for the products in Scheme 2

Ethyl 4-phenylquinoline-2-carboxylate (4a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.5 Hz, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.67–7.47 (m, 6H), 4.58 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 150.0, 148.4, 148.1, 137.8, 131.4, 130.2, 129.8, 128.9, 128.9, 128.8, 128.0, 125.9, 121.5, 62.5, 14.6. The data are consistent with the known literature.[8]

Ethyl 6-methoxy-4-phenylquinoline-2-carboxylate (4b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9.3 Hz, 1H), 8.10 (s, 1H), 7.66–7.48 (m, 5H), 7.44 (dd, J = 9.3, 2.8 Hz, 1H), 7.22 (d, J = 2.8 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 5,7-dimethyl-4-phenylquinoline-2-carboxylate (4c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.93 (s, 1H), 7.52–7.41 (m, 3H), 7.39–7.31 (m, 2H), 7.23 (s, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.53 (s, 3H), 2.01 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 6-bromo-4-phenylquinoline-2-carboxylate (4d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 1H), 8.15 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 7.93–7.82 (m, 1H), 7.66–7.46 (m, 5H), 4.58 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Ethyl 6-chloro-4-phenylquinoline-2-carboxylate (4e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9.0 Hz, 1H), 8.16 (s, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.86–7.72 (m, 1H), 7.72–7.42 (m, 5H), 4.58 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H). The data are consistent with the known literature.[8]

Methyl 6-methyl-4-phenylquinoline-2-carboxylate (4g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.13 (s, 1H), 7.73 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.60–7.50 (m, 5H), 4.09 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 149.3, 147.0, 146.8, 139.3, 137.9, 132.7, 131.0, 129.8, 128.9, 128.9, 128.1, 124.7, 121.7, 53.4, 22.2; IR ν_{max} 3055, 2955, 1731, 1620, 1571, 1492, 1433, 1281, 1231, 1152, 1114, 1002, 830, 760,

705 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{15}NO_2$ $[M + H]^+$ 278.1176, found 278.1177.

Isopropyl 6-methyl-4-phenylquinoline-2-carboxylate (4h). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.05 (s, 1H), 7.69 (s, 1H), 7.62 (dd, J = 8.7, 1.4 Hz, 1H), 7.60–7.49 (m, 5H), 5.45–5.37 (m, 1H), 2.50 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 149.0, 147.5, 147.2, 139.0, 138.2, 132.4, 131.2, 129.8, 128.9, 128.8, 128.0, 124.5, 121.5, 70.0, 22.2, 22.1; IR ν_{max} 2978, 2923, 1707, 1623, 1493, 1373, 1251, 1206, 1104, 1031, 843, 820, 792 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{19}NO_2$ $[M + H]^+$ 306.1489, found 306.1493.

***tert*-Butyl 6-methyl-4-phenylquinoline-2-carboxylate (4i).** ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.68 (s, 1H), 7.65–7.45 (m, 6H), 2.50 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 148.9, 148.3, 147.1, 138.9, 138.3, 132.3, 131.3, 129.8, 128.8, 128.7, 127.8, 124.5, 121.4, 82.7, 28.4, 22.2; IR ν_{max} 2978, 2922, 2853, 1777, 1714, 1620, 1518, 1366, 1147, 1107, 899, 820, 751 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{21}NO_2$ $[M + H]^+$ 320.1645, found 320.1644.

Isobutyl 6-methyl-4-phenylquinoline-2-carboxylate (4j). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.07 (s, 1H), 7.70 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.61–7.48 (m, 5H), 4.29 (d, J = 6.9 Hz, 2H), 2.50 (s, 3H), 2.26–2.12 (m, 1H), 1.06 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 149.1, 147.2, 147.2, 139.1, 138.1, 132.5, 131.2, 129.8, 128.9, 128.8, 128.0, 124.6, 121.5, 72.2, 28.1, 22.2, 19.4; IR ν_{max} 3057, 2962, 2873, 1736, 1616, 1578, 1483, 1464, 1275, 1224, 1104, 997, 893, 826, 766, 700 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{21}NO_2$ $[M + H]^+$ 320.1645, found 320.1644.

Benzyl 6-methyl-4-phenylquinoline-2-carboxylate (4k). ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.7 Hz, 1H), 8.09 (s, 1H), 7.70 (s, 1H), 7.63 (dd, J = 8.7, 1.7 Hz, 1H), 7.60–7.46 (m, 7H), 7.43–7.32 (m, 3H), 5.55 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 149.2, 147.1, 146.9, 139.3, 138.0, 136.0, 132.6, 131.2, 129.8, 128.9, 128.8, 128.6, 128.1, 124.6, 121.7, 67.8, 22.2; IR ν_{max} 3026, 2971, 1738, 1709, 1588, 1546, 1456, 1389, 1352, 1246, 1144, 1108, 989, 896, 825, 751 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{24}H_{19}NO_2$ $[M + H]^+$ 354.1489, found 354.1490.

Phenyl 6-methyl-4-phenylquinoline-2-carboxylate (4l). ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.7 Hz, 1H), 8.24 (s, 1H), 7.76 (s, 1H), 7.68 (dd, J = 8.7, 1.7 Hz, 1H), 7.64–7.52 (m, 5H), 7.51–7.41 (m, 2H), 7.40–7.30 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 151.4, 149.4, 147.2, 146.3, 139.7, 137.9, 132.8, 131.2, 129.8, 129.7, 128.9, 128.3, 126.3, 124.7, 122.1, 122.0, 22.3; IR ν_{max} 2971, 2920, 2220, 1729, 1590, 1496, 1357, 1231, 1186, 1088, 987, 918, 817, 792, 722 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{23}H_{17}NO_2$ $[M + H]^+$ 340.1332, found 340.1334.

Allyl 6-methyl-4-phenylquinoline-2-carboxylate (4m). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 1H), 8.11 (s, 1H), 7.72 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.60–7.49 (m, 5H), 6.22–6.06 (m, 1H), 5.48 (d, J = 17.2 Hz, 1H), 5.34 (d, J = 10.4 Hz, 1H), 5.00 (d, J = 5.8 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 149.2, 147.1, 146.9, 139.3, 138.0, 132.6, 132.2, 131.2, 129.8, 128.9, 128.8, 128.1, 124.6, 121.7, 119.4, 66.9, 22.2; IR ν_{max} 3059, 2921, 1709, 1581, 1486, 1445, 1369, 1278, 1114, 946, 896, 817, 757, 697 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{17}NO_2$ $[M + H]^+$ 304.1332, found 304.1335.

***N*,6-Dimethyl-4-phenylquinoline-2-carboxamide (4n).** ^1H NMR (300 MHz, $CDCl_3$) δ 8.37–8.16 (m, 2H), 8.07 (d, J = 8.6 Hz, 1H), 7.74 (s, 1H), 7.68–7.44 (m, 6H), 3.13 (d, J = 5.1 Hz, 3H), 2.50 (s, 3H). The data are consistent with the known literature.[8]

***N*,6-Dimethyl-4-(*p*-tolyl)quinoline-2-carboxamide (4o).** ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 4.1 Hz, 1H), 8.22 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.76 (s, 1H), 7.59 (dd, J = 8.6, 1.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 3.12 (d, J = 5.1 Hz, 3H), 2.56–2.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 149.5, 148.8, 146.0, 138.6, 138.1, 135.2, 132.3, 129.9, 129.7, 129.51, 128.0, 125.0, 119.3, 26.4, 22.2, 21.5; IR ν_{max} 3323, 2918, 2851, 1671, 1655, 1555, 1499, 1393, 1370, 1254, 1134, 1023, 904, 829 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{18}N_2O$ $[M + H]^+$ 291.1492, found 291.1494.

4-(4-Chlorophenyl)-*N*,6-dimethylquinoline-2-carboxamide (4p). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 4.4 Hz, 1H), 8.20 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.61 (dd, J = 8.6, 1.7 Hz, 1H), 7.55–7.51 (m, 2H), 7.50–7.44 (m, 2H), 3.12 (d, J = 5.1 Hz, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4, 148.8, 148.1, 145.9, 138.6, 136.7, 135.9, 132.5, 131.1, 130.0, 129.1, 127.7, 124.5, 119.3, 26.5, 22.2; IR ν_{max} 3329, 2919, 2850, 1659, 1603, 1533, 1487, 1393, 1252, 1133, 1091, 1016, 904, 843, 824, 754 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{15}ClN_2O$ $[M + H]^+$ 311.0946, found 311.0951.

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