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Copper-Catalyzed Tandem Reaction of Isocyanides with *N*-(2-Haloaryl)propiolamides for the Synthesis of Pyrrolo[3,2-*c*]quinolin-4-ones

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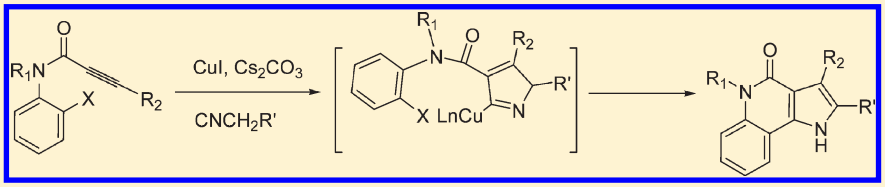
Supporting Information

ABSTRACT:



The copper-catalyzed tandem reaction of isocyanides with *N*-(2-haloaryl)propiolamides is very efficient for the synthesis of pyrrolo[3, 2-*c*]quinolin-4-ones. Highly reactive cyclic organocopper intermediates were proposed to be generated in the copper-catalyzed formal [3 + 2] cycloaddition reaction of isocyanides with triple bonds. Intramolecular trapping of the organocopper intermediates can lead to aryl C−C bond formation, which offered an efficient method for constructing fused pyrrole structures.

INTRODUCTION

Isocyanide compounds have been extensively explored in tandem or multicomponent reactions because of their unusual reactivities to form multiple bonds in a one-pot manner with remarkable versatility in producing structurally appealing heterocycles.[1] Since the initial discoveries by Schöllkopf and Gerhart about 40 years ago,[2] α-metalated isocyanides have been used in various types of cyclization reactions.[1−3] Recently, great progress has been made in the use of transition-metal-catalyzed reactions of isocyanides with double or triple bonds.[4,5] For example, de Meijere et al.[5e] and Yamamoto et al.[5f] independently reported the synthesis of oligosubstituted pyrroles by using copper-catalyzed cycloaddition reactions of isocyanides and alkynes. The reaction was proposed to go through a formal [3 + 2] process and generate a highly reactive organocopper intermediate, which undergoes rapid protonation to form the stable cyclic protonated product. No extension of the highly active organocopper intermediate was reported, perhaps because the organocopper intermediate is too reactive to live long enough for further transformation.[6]

In the past decades, research on copper-catalyzed coupling reactions of aryl halides with nucleophiles came into a renaissance and led to efficient formation of aryl C−C and C−heteroatom bonds.[7] During our continued efforts on copper-catalyzed coupling chemistry,[8] we have realized that the organocopper intermediate produced in the cycloaddition of isocyanide with double or triple bonds may also act as an effective substrate for further aryl C−C coupling. Based on this hypothesis, in a previous communication,[8a] we reported the design and development of the novel copper-catalyzed tandem reaction of isocyanides and 1-(2-haloaryl) ynones, which offered an efficient method for the synthesis of 4-oxoindeno[1,2-*b*]pyrroles. Further exploration revealed that the catalytic system was also applicable to the tandem reactions of isocyanides with *N*-(2-haloaryl)propiolamides. This produced pyrrolo[3,2-*c*]quinolin-4-ones, which and its analogue tricyclic system had been found in biologically active natural products such as martinelline and martinellic acid[9,10] and also known as one of the most widely used motifs in medicinal chemistry for developing potent gastric (H^+/K^+) ATPase inhibitors,[11] antitumor[12] and hypotensive agents,[13] etc. Herein we describe the details of our finding.

RESULTS AND DISCUSSION

Tandem Reaction of Isocyanides with *N*-(2-Haloaryl)propiolamides. In our previous paper, we found that the combination of CuI, Cs_2CO_3, and DMF at 90 °C was the best choice for the copper-catalyzed tandem reactions of isocyanides with 1-(2-iodoaryl)ynones. Under such conditions, we first tested the reaction of *N*-(2-iodophenyl)-3-phenylpropiolamide **1a** with ethyl isocyanoacetate **2a**. As shown in Table 1, no desired product **3a** was detected, and the only isolated product was the protonated pyrrole **4a** (Table 1, entry 1). This observation may be explained with the fact that the C−Cu bond may be readily protonated by the proton attached to the nitrogen atom. In order to overcome this problem, we synthesized a series of *N*-substituted substrates according to the reported methods[14] and

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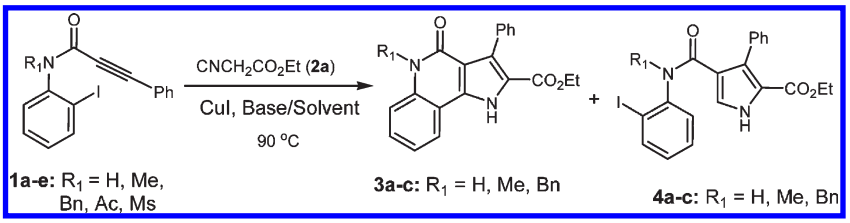
Table 1. Screening of Copper-Catalyzed Reaction Conditions of *N*-(2-Iodophenyl) propiolamides with Ethyl Isocyanoacetate[a]



				yield[b] (%)	
entry	substrate	solvent	base	3	4
1	**1a**	DMF	Cs_2CO_3	n.d.[c]	81
2	**1b**	DMF	Cs_2CO_3	87	8
3	**1c**	DMF	Cs_2CO_3	89	8
4	**1d**	DMF	Cs_2CO_3	45[d]	[e]
5	**1e**	DMF	Cs_2CO_3	52[d]	[e]
6	**1b**	DMSO	Cs_2CO_3	68	28
7	**1b**	dioxane	Cs_2CO_3	16	72
8	**1b**	DMF	K_2CO_3	25	32
9	**1b**	DMF	K_3PO_4	26	36

[a] Reagents and conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (0.55 mmol, 1.1 equiv), CuI (10 mol %), base, (1.0 mmol, 2.0 equiv), solvent (1 mL), 10 min. [b] Isolated yields. [c] No desired product was detected. [d] The isolated product was **3a**. [e] The byproduct **4a** was detected but not isolated.

tested them (Table 1, entries 2−5) under the above reaction conditions. As expected, the reactions of *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1b** and *N*-benzyl-*N*-(2-iodophenyl)-3-phenylpropiolamide **1c** with ethyl isocyanoacetate proceeded smoothly and delivered the desired products **3b** and **3c**, respectively, in high yields, accompanied by about 10% of protonated byproducts **4b** and **4c**, while other *N*-substituted substrates such as *N*-acetyl-*N*-(2-iodophenyl)-3-phenylpropiolamide **1d** and *N*-(2-iodophenyl)-*N*-(methylsulfonyl)-3-phenylpropiolamide **1e** gave the *N*-deprotected product **3a** in moderate yields. When *N*-(2-iodophenyl)-*N*-methyl-3-phenylpropiolamide **1b** was reacted with ethyl isocyanoacetate, other solvents and bases were also screened and all gave reduced outcome (Table 1, entries 6−9).

The structures of the pyrrolo[3,2-*c*]quinolin-4-ones produced in these reactions were identified by comparison with that of **3b** , whose structure was unambiguously determined using X-ray crystallographic analysis.[15]

In addition, the substrate scope was explored, and the results are shown in Table 2. In most cases, the tandem reactions of isocyanides with *N*-methyl-*N*-(2-iodoaryl)propiolamides afforded the desired products in moderate or good yields. Both the alkyl and aryl substituents on the alkyne moiety were well tolerated, and the corresponding tandem reaction products were delivered in high yields. Electron-withdrawing substituents such as −CN, $-CF_3$, and $-NO_2$ on the 2-iodoaryl ring greatly enhanced the reactivities as compared with electron-donating substituents such as methyl or methoxy groups (Table 2, entries 7 and 8). The yields of the latter substrates were greatly improved at more elevated reaction temperatures. Furthermore, the reactions of *tert*-butyl isocyanoacetate **2b** and benzyl isocyanide **2c** with *N*-(2-iodophenyl)-*N*-methylhept-2-ynamide **5b** proceeded smoothly and delivered the desired products in high yields (Table 2, entries 12 and 13). However, diethyl isocyanomethylphosphonate **2d** and tosylmethyl isocyanide **2e** delivered the corresponding products only in low yields at 90 °C (Table 2, entries 14 and 15).

For less reactive *N*-methyl-*N*-(2-bromoaryl)propiolamide substrates, low yields were obtained, and no improvements were observed even at 130 °C (Table 2, entries 5 and 6).

Synthesis of Pyrrolo[3,2-*c*]quinolin-4-ones through Combination of Ugi-4-CR and the Copper-Catalzyed Reactions. In order to increase the reaction diversity and structural complexity, we extended the reaction to a two-step process involving a Ugi four-component reaction[1,16] and the copper-catalyzed tandem reaction. Thus, *N*-(2-iodoaryl)propiolamide derivatives **11a**−**g** were synthesized through Ugi-4-CR at room temperature in methanol. After the solvent was evaporated, the residues were directly used for the copper-catalyzed tandem reactions to deliver the corresponding products under the optimized conditions. Although only 20−35% yields of the desired products were obtained at 90 °C, the yields were increased to about 35−65% when the reaction temperature was elevated to 130 °C. As shown in Table 3, a series of pyrrolo[3,2-*c*]quinolines were synthesized through the two-step procedure. In addition, all of the starting materials for the two-step reactions were commercially available and the reactions were easy to handle, which offered a simple way to increase the product diversity and structural complexity.

Tandem Reactions of Isocyanides with 2-Iodophenyl Propiolates. Based on the above novel tandem reactions of isocyanides with *N*-(2-haloaryl)propiolamides, we expected that similar results may be obtained using 2-haloaryl propiolates as substrates. However, when we tested the reaction of ethyl isocyanoacetate **2a** with 2-iodophenyl 3-phenylpropiolate **13a** or 2-iodophenyl hept-2-ynoate **13b**, only a trace amount of the desired products **14a/b** were detected (Scheme 1). The isolated products were mainly protonated byproducts **15a/b** and **16a/b**. We speculated that the byproducts **16a/b** were derived from the protonated byproducts **15a/b** through another cyclization of its 2-iodophenyl ester group with ethyl isocyanoacetate. In addition, a similar result was obtained when these reactions were performed at room temperature.

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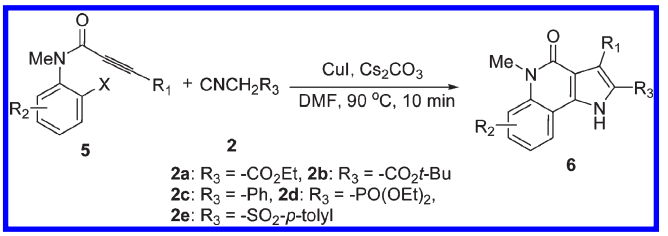
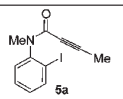
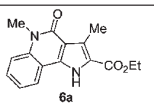
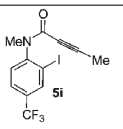
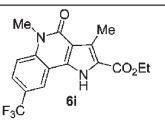
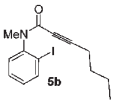
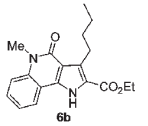
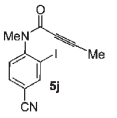
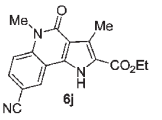
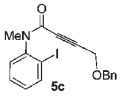
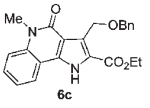
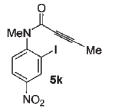
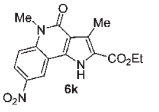
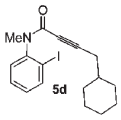
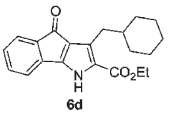
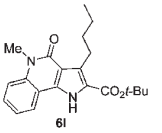
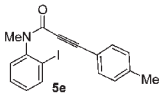
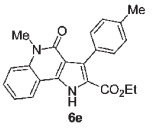
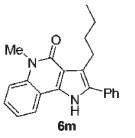
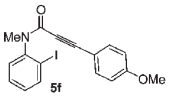
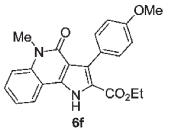
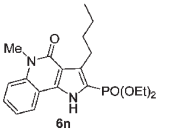
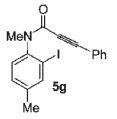
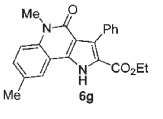
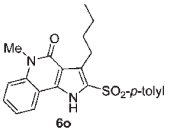
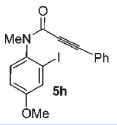
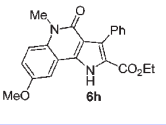
Table 2. Copper-Catalyzed Tandem Reaction of Isocyanides with *N*-Methyl-*N*-(2-haloaryl)propiolamides[a]



entry	substrate 2	product	yield (%) [b]	entry	substrate 2	product	yield (%) [b]
1			65	9			81
2			87	10			76
3			72	11			75
4			85	12	**5b**		80
5			84 (32) [c]	13	**5b**		72
6			76 (30) [c]	14	**5b**		35
7			50 (73) [d]	15	**5b**		15
8			35 (77) [d]				

[a] Reagents and conditions: isocyanides used: entries 1−11, **2a**; entry 12, **2b**; entry 13, **2c**; entry 14, **2d**; entry 15, **2e**. 90 °C, 10 min. X = I unless otherwise indicated. [b] Isolated yields. [c] X = Br. [d] 130 °C.

Plausible Mechanism. The mechanism of copper-catalyzed reactions of isocyanides with alkynes has been well described.[5e,f] Based on the literature precedent and experimental observations, we put forward a plausible catalytic cycle for the tandem reaction of *N*-(2-haloaryl)propiolamides with isocyanides as depicted in Scheme 2. In this pathway, reaction of the isocyanide with CuI in

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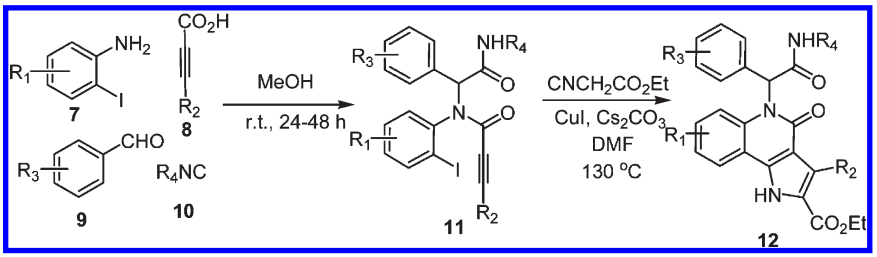
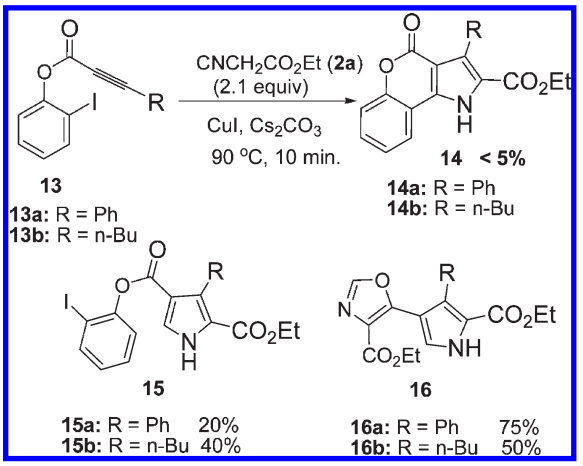
Table 3. Two-Step Synthesis of Pyrrolo[3,2-*c*]quinolin-4-ones through Ugi-4-CR and Copper-Catalyzed Reaction[a]



entry	R_1	R_2	R_3	R_4	product	yield[b] (%)
1	H	Ph	4-Me	*t*-Bu	**12a**	54
2	H	n-Pr	4-Me	*t*-Bu	**12b**	65
3	H	n-Pr	4-Me	cyclohexyl	**12c**	40
4	H	Me	4-Me	*t*-Bu	**12d**	40
5	H	n-Pr	4-Cl	*t*-Bu	**12e**	61
6	H	Ph	H	*t*-Bu	**12f**	55
7	4-Cl	n-Pr	4-Me	*t*-Bu	**12g**	35

[a] Reagents and conditions: **7** (0.5 mmol), **8** (0.5 mmol), **9** (0.5 mmol), **10** (0.5 mmol), methanol (1 mL), 24−48 h; then in DMF (1.0 mL), CuI (10 mol %), Cs_2CO_3 (1.0 mmol), **2a** (0.6 mmol), 130 °C, 10 min. [b] Yields for two steps.

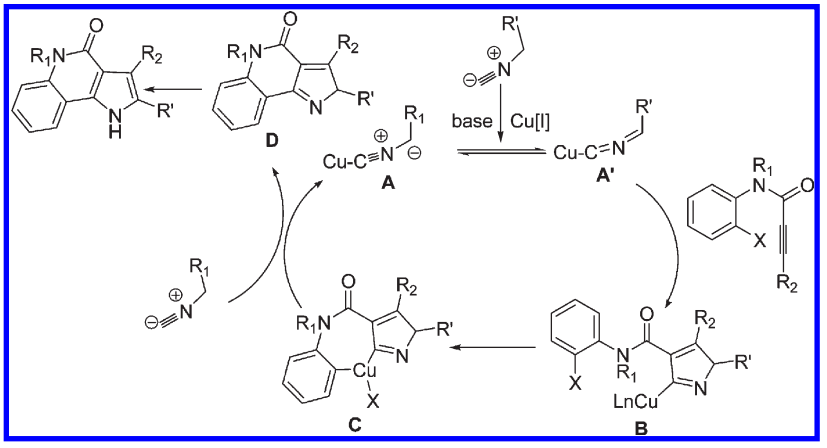
Scheme 1. Copper-Catalyzed Reaction of Ethyl Isocyanoacetate (2a) with 2-Iodophenyl Propiolates



the presence of base forms the α-cuprioisocyanide **A** or its tautomer **A′**. This intermediate reacts through a formal [3 + 2] cycloaddition process with the *N*-(2-haloaryl)propiolamides to generate the cyclic organocopper intermediate **B**. Through intramolecular insertion of Cu into the aryl C−X bond, intermediate **B** is then transformed to intermediate **C**. Intermediate D along with A or A′ are then generated from **C** to end the catalytic cycle. Finally, pyrrolo[3,2-*c*]quinolin-4-one products are produced by tautomerization.

In conclusion, we successfully developed a novel, simple and efficient method for the synthesis of pyrrolo[3,2-*c*]quinolin-4-ones. The method is based on the copper-catalyzed reaction of isocyanides with *N*-(2-haloaryl)propiolamide through a tandem formal [3 + 2] cycloaddtion/coupling process. The process took place efficiently when a variety of *N*-(2-iodoaryl)propiolamides were used, and it displayed a wide range of functional group compatibility. Furthermore, a combination of Ugi-4-CR and the copper-catalyzed protocol simplified the reaction and increased the structural complexity in the products. Further studies and

Scheme 2. Plausible Mechanism for Copper-Catalyzed Tandem Reaction of *N*-(2-Haloaryl)propiolamides with Isocyanides



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applications of this methodology are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Procedures. All reactions were carried out in 10 mL tubes. DMF was distilled from CaH_2 and stored on 4 Å activated molecular sieves. Cs_2CO_3 (Alfa Aesar), CuI (Alfa Aesar), and all other solid materials were stored under vacuum at room temperature and weighed in the air. Column chromatography was performed with silica gel (200−400 mesh).

General Procedure for the Synthesis of Pyrrolo[3, 2-*c*]-quinolin-4-ones through Copper-Catalyzed Tandem Reaction. Isocyanides (0.55 mmol) was added to a mixture of cesium carbonate (325 mg, 1.0 mmol, 2.0 equiv), copper iodide (10 mg, 0.05 mmol, 10% equiv), *N*-(2-haloaryl)propiolamides (0.5 mmol, 1.0 equiv) in DMF (1 mL) at 90 °C. The mixture was stirred under air for 10 min. Monitoring with TLC showed that the reaction was complete. Water (5 mL) was added, and the aqueous phase was extracted with ethyl acetate (5 mL × 3). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was loaded on silica column and purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 8:1) to afford the final product.

*Ethyl 4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3a**):* ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.93 (s, 1H), 11.14 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 7.32−7.44 (m, 7H), 7.20 (m, 1H), 4.13 (q, J =7.2 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.2, 159.5, 137.9, 137.0, 133.9, 131.4, 129.8, 129.3, 127.1, 127.0, 123.1, 122.7, 121.8, 116.1, 113.7, 112.5, 60.5, 14.2; ESI-MS m/z 333.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{20}H_{17}N_2O_3^+$ $[M + H]^+$ requires 333.1234, found 333.1236.

*Ethyl 5-methyl-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**3b**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.00 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.53−7.57 (m, 1H), 7.49 (m, 2H), 7.33−7.43 (m, 4H), 7.29 (d, J = 7.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.69 (s, 3H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7, 159.4, 138.9, 135.2, 132.9, 130.9, 130.5, 129.5, 127.4, 127.0, 122.1, 121.8, 121.4, 115.4, 113.9, 112.8, 61.0, 29.0, 13.8; ESI-MS m/z 347.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{21}H_{19}N_2O_3^+$ $[M + H]^+$ requires 347.1390, found 347.1390.

*Ethyl 5-benzyl-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**3c**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.19 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 6.8 Hz, 2H), 7.32−7.40 (m, 4H), 7.23−7.30 (m, 3H), 7.17−7.21 (m, 4H), 5.57 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7, 159.5, 138.3, 137.0, 135.8, 132.7, 131.3, 130.6, 129.5, 128.6, 127.4, 127.0, 126.4, 122.4, 121.8, 121.8, 116.4, 113.5, 113.2, 61.1, 60.4, 45.4, 13.8; ESI-MS m/z 423.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{27}H_{23}N_2O_3^+$ $[M + H]^+$ requires 423.1703, found 423.1705.

*Ethyl 4-(2-iodophenylcarbamoyl)-3-phenyl-1H-pyrrole-2-carboxylate (**4a**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 3.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.42−7.50 (m, 6H), 7.26−7.31 (m, 1H), 6.77 (t, J = 7.2 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 160.7, 138.9, 138.7, 132.6, 131.1, 128.7, 128.7, 128.7, 128.5, 126.9, 125.8, 123.1, 121.1, 120.9, 89.7, 60.6, 13.9; ESI-MS m/z 461.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{20}H_{18}IN_2O_3^+$ $[M + H]^+$ requires 461.0357, found 461.0360.

*Ethyl 4-((2-iodophenyl)(methyl)carbamoyl)-3-phenyl-1H-pyrrole-2-carboxylate (**4b**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.35 (s, 5H), 7.07−7.10 (m, 1H), 6.89−6.92 (m, 2H), 6.36 (d, J = 6.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.17 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 160.8, 146.1, 139.6, 133.7, 130.6, 130.3, 129.5, 129.2, 129.0, 127.3, 126.9, 122.8, 121.4, 118.5, 99.5, 60.3, 36.8, 14.0; ESI-MS m/z 474.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{21}H_{20}IN_2O_3^+$ $[M + H]^+$ requires 475.0513, found 475.0515.

*Ethyl 4-(benzyl(2-iodophenyl)carbamoyl)-3-phenyl-1H-pyrrole-2-carboxylate (**4c**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.32 (s, 5H), 7.16−7.22 (m, 3H), 7.06−7.07 (m, 2H), 6.97 (s, 1H), 6.81−6.89 (m, 2H), 5.86 (d, J = 6.8 Hz, 1H), 5.73 (d, J = 14.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.96 (d, J = 14.0 Hz, 1H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 160.7, 143.7, 139.5, 136.5, 133.6, 133.5, 131.3, 130.7, 130.1, 129.4, 129.2, 128.4, 128.2, 127.4, 127.3, 122.0, 121.9, 121.7, 121.6, 118.4, 100.6, 60.4, 51.9, 14.0; ESI-MS m/z 551.0 $[M + H]^+$; HR-MS (ESI) calcd for $C_{27}H_{24}IN_2O_3^+$ $[M + H]^+$ requires 551.0826, found 551.0825.

*Ethyl 3,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**6a**):* ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.54 (s, 1H), 8.50 (d, J = 7.5 Hz, 1H), 7.48−7.53 (m, 2H), 7.26 (t, J = 7.0 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 3.60 (s, 3H), 2.69 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.6, 159.9, 138.6, 135.7, 129.4, 126.9, 123.3, 122.5, 122.0, 115.7, 113.6, 113.5, 60.5, 28.8, 14.8, 11.6; ESI-MS m/z 285.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{16}H_{17}N_2O_3^+$ $[M + H]^+$ requires 285.1234, found 285.1230.

*Ethyl 3-butyl-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**6b**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.23−7.26 (m, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.32 (t, J = 8.0 Hz, 2H), 1.60−1.70 (m, 2H), 1.40−1.51 (m, 5H), 0.95 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2, 160.2, 138.8, 135.3, 133.6, 129.2, 121.7, 121.6, 121.3, 115.3, 113.9, 113.0, 60.9, 33.5, 28.9, 25.1, 22.9, 14.4, 14.0; ESI-MS m/z 327.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{19}H_{23}N_2O_3^+$ $[M + H]^+$ requires 327.1703, found 327.1699.

*Ethyl 3-(benzyloxymethyl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo-[3,2-c]quinoline-2-carboxylate (**6c**):* ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.90 (s, 1H), 8.55 (d, J = 8.0 Hz, 1H), 7.55 (s, 2H), 7.25−7.32 (m, 6H), 5.14 (s, 2H), 4.58 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.65 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.8, 158.8, 139.0, 138.1, 135.3, 129.2, 128.0, 127.3, 127.1, 125.2, 124.1, 122.9, 121.7, 115.5, 113.3, 112.9, 71.5, 61.2, 60.5, 28.6, 14.2; ESI-MS m/z 391.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{23}H_{23}N_2O_4^+$ $[M + H]^+$ requires 391.1652, found 391.1649.

*Ethyl 3-(cyclohexylmethyl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo-[3,2-c]quinoline-2-carboxylate (**6d**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.63 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.24−7.26 (m, 1H), 4.43 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.22 (d, J = 6.4 Hz, 2H), 1.81−1.64 (m, 6H), 1.44 (t, J = 7.2 Hz, 3H), 1.11−1.20 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.1, 160.2, 138.9, 135.1, 132.1, 129.2, 122.2, 121.7, 121.1, 115.3, 114.5, 112.9, 60.9, 39.8, 33.1, 32.4, 28.9, 26.6, 26.5, 14.4; ESI-MS m/z 367.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{27}N_2O_3^+$ $[M + H]^+$ requires 367.2016, found 367.2013.

*Ethyl 5-methyl-4-oxo-3-p-tolyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**6e**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.90 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.53−7.57 (m, 1H), 7.38−7.43 (m, 3H), 7.18−7.26 (m, 3H), 4.23 (q, J = 7.2 Hz, 2H), 3.69 (s,3H), 2.38 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.5, 159.4, 138.9, 137.0, 135.1, 131.1, 130.4, 129.5, 129.5, 127.8, 121.9, 121.8, 121.3, 115.4, 113.9, 112.8, 60.9, 28.9, 21.4, 13.9; ESI-MS m/z 361.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{21}N_2O_3^+$ $[M + H]^+$ requires 361.1547, found 361.1545.

*Ethyl 3-(4-methoxyphenyl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo-[3,2-c]quinoline-2- carboxylate (**6f**):* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.07 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.40−7.4 (m, 3H), 7.28−7.29 (m, 1H), 6.93 (d, J = 8.0 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz) 161.7, 159.5, 159.0, 138.9, 135.3, 131.8, 130.8, 129.4, 124.9, 121.9, 121.7, 121.6, 115.3, 113.8, 112.9, 112.5, 61.0, 55.1, 29.0, 14.0; ESI-MS *m/z* 377.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{21}N_2O_4^+$ $[M + H]^+$ requires 377.1496, found 377.1500.

*Ethyl 5,8-dimethyl-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**6g**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 9.93 (s, 1H), 7.70 (s, 1H), 7.48−7.50 (m, 2H), 7.30−7.40 (m, 5H), 4.22 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 2.47 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6, 159.3, 136.9, 135.1, 132.9, 131.4, 130.9, 130.6, 130.5, 127.3, 126.9, 122.0, 121.3, 115.3, 113.9, 112.6, 60.9, 28.9, 20.7, 13.8; ESI-MS *m/z* 361.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{21}N_2O_3^+$ $[M + H]^+$ requires 361.1547, found 361.1549.

*Ethyl 8-methoxy-5-methyl-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo-[3,2-c]quinoline-2-carboxylate (**6h**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 10.65 (s, 1H), 7.59 (d, J = 4.2 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.23−7.27 (m, 3H), 7.14−7.18 (m, 1H), 7.08 (dd, J = 8.0, 2.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8, 159.2, 154.6, 135.4, 133.2, 133.0, 130.8, 130.5, 127.0, 126.8, 122.4, 117.1, 116.5, 113.9, 113.7, 105.0, 60.9, 55.7, 29.0, 13.6; ESI-MS *m/z* 377.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{21}N_2O_4^+$ $[M + H]^+$ requires 377.1496, found 377.1495.

*Ethyl 3,5-dimethyl-4-oxo-8-(trifluoromethyl)-4,5-dihydro-1H-pyrrolo-[3,2-c]quinoline-2-carboxylate (**6i**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 10.12 (s, 1H), 8.20 (s, 1H), 7.72 (d, J =8.4 Hz, 1H), 7.49 (d, J =8.8 Hz, 1H), 4.42 (q, J =7.2 Hz, 2H), 3.75 (s, 3H), 2.71 (br s, 3H), 1.41(t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 160.3, 140.7, 134.4, 128.4, 125.3, 124.0, 123.0, 122.7, 119.1, 115.7, 114.7, 113.0, 61.3, 29.1, 14.2, 11.1; ESI-MS *m/z* 353.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{17}H_{16}F_3N_2O_3^+$ $[M + H]^+$ requires 353.1108, found 353.1110.

*Ethyl 8-cyano-3,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**6j**):* ^1H NMR (DMSO-d_6, 400 MHz) δ 12.62 (s, 1H), 8.95 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.60 (s, 3H), 2.65 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.8, 159.2, 140.7, 133.5, 131.4, 127.3, 126.4, 122.8, 118.8, 116.5, 113.6, 113.4, 103.7, 60.3, 28.7, 14.3, 10.9; ESI-MS *m/z* 310.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{17}H_{16}N_3O_3^+$ $[M + H]^+$ requires 310.1186, found 310.1194.

*Ethyl 3,5-dimethyl-8-nitro-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**6k**):* ^1H NMR (DMSO-d_6, 400 MHz) δ 12.88 (s, 1H), 9.45 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.59 (d, J =8.8 Hz, 1H), 4.35 (q, J =7.2 Hz, 2H), 3.59 (s, 3H), 2.61 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.6, 160.1, 142.7, 141.8, 133.5, 128.4, 123.8, 117.2, 115.7, 115.1, 112.9, 61.3, 29.4, 14.4, 11.1; ESI-MS *m/z* 330.2 $[M + H]^+$; HR-MS (ESI) calcd for $C_{16}H_{16}N_3O_5^+$ $[M + H]^+$ requires 330.1084, found 330.1090.

*tert-Butyl 3-butyl-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]-quinoline-2-carboxylate (**6l**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 9.66 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.21−7.27(m, 1H), 3.73 (s, 3H), 3.28 (t, J = 8.0 Hz, 2H), 1.61−1.68 (m, 11H), 1.43−1.50 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 161.9, 160.3, 138.6, 135.1, 132.4, 128.9, 123.1, 121.7, 121.4, 115.1, 113.7, 113.1, 82.0, 33.7, 28.8, 28.4, 28.3, 28.3, 28.2, 25.3, 23.0, 14.2; ESI-MS *m/z* 355.4 $[M + H]^+$; HR-MS (ESI) calcd for $C_{21}H_{27}N_2O_3^+$ $[M + H]^+$ requires 355.2016, found 355.2021.

*3-Butyl-5-methyl-2-phenyl-1H-pyrrolo[3,2-c]quinolin-4(5H)-one (**6m**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.39−7.47 (m, 3H), 7.32 (t, J = 7.2 Hz, 2H), 7.23−7.26 (m, 1H), 3.74 (s, 3H), 3.02 (t, J = 8.0 Hz, 2H), 1.74−1.78 (m, 2H), 1.37−1.43 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.5, 137.7, 133.7, 132.6, 132.1, 128.8, 127.9, 127.6, 127.4, 121.7, 121.6, 120.1, 115.2, 114.2, 113.8, 34.1, 28.9, 24.8, 22.9, 13.9; ESI-MS *m/z* 331.4 $[M + H]^+$; HR-MS (ESI) calcd for $C_{22}H_{23}N_2O^+$ $[M + H]^+$ requires 331.1805, found 331.1804.

*Diethyl 3-butyl-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]-quinolin-2-ylphosphonate (**6n**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 11.57 (s, 1H), 8.40 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 4.20−4.26 (m, 4H), 3.76 (s, 3H), 3.07 (t, J = 8.0 Hz, 2H), 1.69−1.79 (m, 2H), 1.48−1.55 (m, 2H), 1.35 (t, J = 7.2 Hz, 6H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.3, 138.6, 137.4, 137.3, 135.0, 134.9, 128.7, 122.4, 121.5, 118.4, 116.6, 115.1, 114.0, 113.8, 62.5, 62.5, 33.8, 28.9, 25.6, 23.2, 16.3, 16.2, 14.0; ESI-MS *m/z* 391.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{20}H_{28}N_2O_4P^+$ $[M + H]^+$ requires 391.1781, found 391.1781.

*3-Butyl-5-methyl-2-tosyl-1H-pyrrolo[3,2-c]quinolin-4(5H)-one (**6o**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 9.75 (s, 1H), 7.85−7.88 (m, 3H), 7.51−7.55 (m, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.26−7.32 (m, 3H), 3.71 (s, 3H), 3.07 (t, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.38−1.43 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.6, 144.5, 139.0, 138.9, 135.4, 131.6, 130.0, 129.7, 127.4, 127.1, 122.0, 121.3, 115.4, 114.2, 112.6, 32.9, 29.0, 24.7, 23.1, 21.6, 13.9; ESI-MS *m/z* 409.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{23}H_{25}N_2O_3S^+$ $[M + H]^+$ requires 409.1580, found 409.1574.

General Procedure for the Two-Step Synthesis of Pyrrolo-[3, 2-*c*]quinolin-4-ones through Ugi-4-CR and Copper-Catalyzed Reactions. 2-Iodoaniline **7** (0.5 mmol) and benzaldehyde **9** (0.5 mmol) were mixed together in MeOH (5 mL) and stirred for 30 min. Then acid **8** (0.5 mmol) and, after 15 min, isocyanide **10** (0.5 mmol) were added. The mixture was stirred for 24 h. After removal of the solvent, cesium carbonate (325 mg, 1.0 mmol, 2.0 equiv), copper iodide (10 mg, 0.05 mmol, 10% equiv), ethyl isocyanoacetate **2a** (0.56 mmol, 1.2 equiv), and DMF (1 mL) were added to Ugi adduct **11** in the flask. The mixture was stirred at 130 °C for 10 min. After being cooled to room temperature, the reaction mixture was diluted with brine and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated in vacuum. The residues were purified by column chromatography on silica gel to give the desired products as white solids.

*Ethyl 5-(2-(tert-butylamino)-2-oxo-1-p-tolylethyl)-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12a**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 11.80 (br s, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 5.2 Hz, 2H), 7.26−7.31 (m, 5H), 7.08−7.12 (m, 3H), 7.01−7.04(m, 1H), 6.92 (br s, 1H), 6.37 (br s, 1H), 5.66 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.42 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 161.4, 159.8, 138.2, 137.8, 136.1, 132.4, 132.0, 131.6, 130.3, 129.6, 128.5, 128.0, 127.0, 126.2, 122.7, 122.5, 122.1, 113.5, 113.1, 60.3, 52.0, 28.4, 21.1, 14.1; ESI-MS *m/z* 536.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{33}H_{34}N_3O_4^+$ $[M + H]^+$ requires 536.2544, found 536.2543.

*Ethyl 5-(2-(tert-butylamino)-2-oxo-1-p-tolylethyl)-4-oxo-3-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12b**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 7.2 Hz, 1H), 7.33 (d, J = 7.2 Hz, 2H), 7.18 (d, J = 7.2 Hz, 2H), 7.07−7.11 (m, 1H), 6.98−7.02 (m, 1H), 6.90 (br s, 1H), 6.28 (br s, 1H), 5.77 (s, 1H), 4.35−4.49 (m, 2H), 3.11 (m, 1H), 2.81 (m, 1H), 2.34 (s, 3H), 1.43−1.62 (m, 14H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 161.9, 160.5, 138.2, 137.8, 135.9, 133.3, 132.3, 129.7, 128.2, 127.7, 122.7, 122.0, 121.9, 115.5, 113.8, 113.5, 60.2, 51.9, 28.5, 27.2, 24.4, 21.0, 14.5, 14.1; ESI-MS *m/z* 502.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{30}H_{35}N_3O_4Na^+$ $[M + Na]^+$ requires 524.2520, found 524.2512

*Ethyl 5-(2-(cyclohexylamino)-2-oxo-1-p-tolylethyl)-4-oxo-3-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12c**):* ^1H NMR ($CDCl_3$, 400 MHz) δ 11.45 (br s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.97 (br s, 1H), 6.43 (s, 1H), 5.83 (d, J = 8.0 Hz, 1H), 4.34−4.49 (m, 2H), 3.91−3.99 (m, 1H), 3.13 (m, 2H), 2.84 (m, 1H), 2.33 (s, 3H), 2.15 (d, J = 10.8 Hz, 1H), 1.85 (d, J = 10.0 Hz, 1H), 1.72(d, J = 13.2 Hz, 1H), 1.53−1.62 (m, 3H), 1.46 (t, J = 7.2 Hz,

3H), 1.32−1.42 (m, 2H), 1.10−1.27(m, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 162.1, 160.4, 138.0, 137.9, 136.0, 133.0, 132.2, 129.8, 128.4, 127.5, 123.0, 122.1, 122.0, 115.2, 113.9, 113.4, 60.2, 49.1, 32.5, 32.3, 27.2, 25.7, 24.8, 24.7, 24.4, 21.1, 14.5, 14.1; ESI-MS m/z 528.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{32}H_{38}N_3O_4^+$ $[M + H]^+$ requires 528.2857, found 528.2860.

5-(2-(tert-Butylamino)-2-oxo-1-p-tolylethyl)-3-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12d**): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.62 (br s, 1H), 8.46 (d, J = 7.2 Hz, 1H), 7.53 (s, 1H), 7.28 (m, 1H), 7.05−7.21 (m, 7H), 4.38 (q, J = 7.2 Hz, 2H), 2.73 (s, 3H), 2.23 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.24 (s, 9H); ^{13}C NMR (DMSO, 125 MHz) δ 167.6, 161.6, 160.7, 137.7, 136.5, 136.3, 134.1, 129.2, 128.0, 127.9, 127.3, 123.1, 122.7, 122.0, 119.2, 114.2, 113.3, 60.6, 51.2, 28.8, 21.0, 14.8, 11.7; ESI-MS m/z 474.4 $[M + H]^+$; HR-MS (ESI) calcd for $C_{28}H_{32}N_3O_4^+$ $[M + H]^+$ requires 474.2387, found 474.2379.

Ethyl 5-(2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl)-4-oxo-3-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12e**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 7.6 Hz, 1H), 7.33−7.40 (m, 4H), 7.12 (t, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.92 (br s, 1H), 6.45 (br s, 1H), 5.70 (s, 1H), 4.34−4.50 (m, 2H), 3.13−3.16 (m, 1H), 2.86 (m, 1H), 1.52−1.62 (m, 2H), 1.47 (t, J = 7.2 Hz, 3H), 1.40 (s, 9H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 162.0, 160.5, 137.7, 135.9, 133.8, 133.8, 133.2, 129.7, 129.0, 128.1, 122.4, 122.2, 113.8, 113.4, 60.5, 53.3, 52.0, 28.5, 27.2, 24.4, 14.5, 14.1; ESI-MS m/z 522.0 $[M + H]^+$; HR-MS (ESI) calcd for $C_{29}H_{33}ClN_3O_4^+$ $[M + H]^+$ requires 522.2160, found 522.2163.

Ethyl 5-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-4-oxo-3-phenyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12f**): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.56 (d, J = 6.8 Hz, 1H), 7.54 (s, 1H), 7.42 (d, J = 3.6 Hz, 2H), 7.26−7.32 (m, 6H), 7.14−7.22 (m, 5H), 7.03 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.23 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 167.5, 161.1, 159.5, 137.8, 137.2, 136.4, 133.7, 131.4, 130.2, 128.6, 128.1, 128.0, 127.3, 127.1, 126.9, 123.2, 123.0, 122.1, 119.1, 114.0, 112.6, 60.6, 59.0, 51.2, 28.8, 14.2; ESI-MS m/z 544.3 $[M + H]^+$; HR-MS (ESI) calcd for $C_{32}H_{31}N_3NaO_4^+$ $[M + H]^+$ requires 544.2207, found 544.2200.

Ethyl 5-(2-(tert-butylamino)-2-oxo-1-p-tolylethyl)-8-chloro-4-oxo-3-propyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (**12g**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 7.31 (d, J = 6.8 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 7.6 Hz, 1H), 6.74 (br s, 1H), 5.82 (s, 1H), 4.40−4.49 (m, 2H), 3.18−3.25(m, 1H), 2.81 (m, 1H), 2.35(s, 3H), 1.48−1.52 (m, 11H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 161.8, 159.9, 138.3, 136.6, 134.5, 133.5, 132.1, 130.0, 128.4, 127.6, 127.2, 122.9, 122.4, 116.0, 115.2, 113.7, 64.0, 60.2, 52.3, 28.5, 27.0, 24.4, 21.1, 14.6, 14.0; ESI-MS m/z 558.3 $[M + Na]^+$; HR-MS (ESI) calcd for $C_{30}H_{34}ClN_3NaO_4^+$ $[M + Na]^+$ requires 558.2130, found 558.2122.

General Procedure for the Tandem Reactions of Ethyl Isocyanoacetate 2a with 2-Iodophenyl Propiolates 13a/b. Ethyl isocyanoacetate **2a** (1.05 mmol, 2.1 equiv) was added to a mixture of cesium carbonate (325 mg, 1.0 mmol, 2.0 equiv), copper iodide (10 mg, 0.05 mmol, 10% equiv), and 2-iodophenyl propiolate **13a/b** (0.5 mmol, 1.0 equiv) in DMF (1 mL) at 90 °C. The mixture was stirred under air for 10 min. Monitoring with TLC showed that the reaction was complete. Water (5 mL) was added, and the aqueous phase was extracted with ethyl acetate (5 mL × 3). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The residue was loaded on silica column and purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 8:1) to afford final product **15** and **16**.

2-Ethyl 4-(2-iodophenyl) 3-phenyl-1H-pyrrole-2,4-dicarboxylate (**15a**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.71 (br s, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 6.8 Hz, 2H), 7.28−7.36 (m, 4H), 7.14 (d, J = 8.0 Hz, 1H), 6.90−6.94 (m, 1H), 4.12−4.20 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 160.6, 150.9, 139.2, 133.1, 132.7, 130.3, 129.1, 128.2, 127.4, 127.2, 127.1, 123.4, 121.5, 115.4, 90.6, 60.7, 13.8; ESI-MS m/z 462.0 $[M + H]^+$; HR-MS (ESI) calcd for $C_{20}H_{17}INO_4^+$ $[M + H]^+$ requires 462.0197, found 462.0199.

2-Ethyl 4-(2-iodophenyl) 3-propyl-1H-pyrrole-2,4-dicarboxylate (**15b**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.44 (br s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.37−7.41 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 6.97−7.00 (m, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.13 (t, J = 7.6 Hz, 2H), 1.62−1.67(m, 2H), 1.40 (t, J = 7.2 Hz, 3H); 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.4, 161.3, 151.0, 139.3, 135.6, 129.3, 128.4, 127.3, 123.5, 121.1, 114.9, 90.8, 60.7, 27.0, 24.3, 14.3, 14.1; ESI-MS m/z 428.0 $[M + H]^+$; HR-MS (ESI) calcd for $C_{17}H_{19}INO_4^+$ $[M + H]^+$ requires 428.0353, found 428.0350.

Ethyl 5-(5-(ethoxycarbonyl)-4-phenyl-1H-pyrrol-3-yl)oxazole-4-carboxylate (**16a**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.64(br s, 1H), 7.99(d, J = 3.2 Hz, 1H), 7.55 (s, 1H), 7.27−7.32 (m, 5H), 4.38 (q, J = 7.2 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H); 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2, 161.1, 152.2, 148.6, 140.0, 130.6, 130.2, 127.2, 127.1, 126.0, 125.8,120.4, 115.3, 61.1, 60.5, 14.3, 13.8; ESI-MS m/z 355.1 $[M + H]^+$; HR-MS (ESI) calcd for $C_{19}H_{19}N_2O_5^+$ $[M + H]^+$ requires 355.1288, found 355.1286.

Ethyl 5-(5-(ethoxycarbonyl)-4-propyl-1H-pyrrol-3-yl)oxazole-4-carboxylate (**16b**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29(br s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 4.35−4.40 (m, 4H), 2.99 (t, J = 7.2 Hz, 2H), 1.55−1.62 (m, 2H), 1.37−42 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H); 13C NMR ($CDCl_3$, 125 MHz) δ 162.2, 161.3, 153.0, 148.0, 132.0, 126.0, 120.2, 111.3, 61.1, 60.4, 27.5, 24.4, 14.4, 14.3, 14.1; ESI-MS m/z 321.0 $[M + H]^+$; HR-MS (ESI) calcd for $C_{16}H_{21}N_2O_5^+$ $[M + H]^+$ requires 321.1445, found 321.1440.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}HNMR and ^{13} C NMR spectra for all new products and crystallographic data for **3b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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