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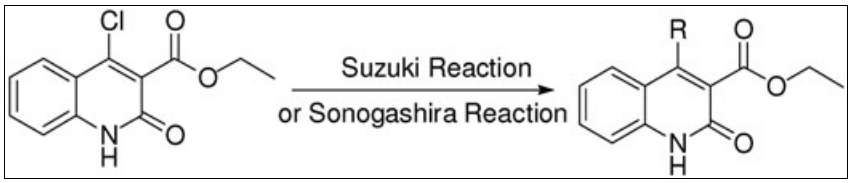

An efficient route for the synthesis of 4-substituted-2-quinolinone-3-carboxylic acid ethyl esters has been developed through Suzuki or Sonogashira reactions. The advantages of the method include high yields, operational simplicity, and suitability for medicinal modification of 4-substituted quinolinones and their derivatives.

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INTRODUCTION

Quinolinones are an important class of heteroaromatic compounds. Because of their wide spectrum of pharmacological applications, much more attention is focused on development of new members [1]. Among them, 4-substituted-2-quinolinone is one of the scaffolds that exhibit various biological activities (Scheme 1). For instance, quinolin-2(1H)-one derivatives **1** were found as potent inducible nitric oxide synthase inhibitors [2], 4-aryl-3-(3-aryl-1-oxo-2-propenyl)-2(1H)-quinolinones **2** were apoptosis inducers in human cancer cells [3], and 3,4,6-substituted-2-quinolones **3** were considered as FMS kinase inhibitors [4].

Several methods have been reported in the literature for the synthesis of 4-substituted-2-quinolinones [4,5] (Scheme 2). Among them, the general method was that the 4-position substituent on the quinolinone ring was introduced first before the formation of quinolinone ring. However, this method limited the diversity of the 4-position substituent of quinolinone, because the processes were always repeated.

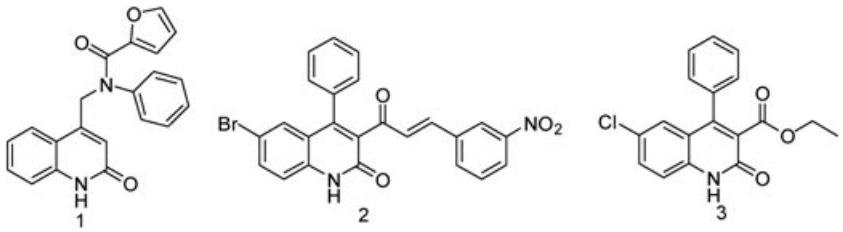
From the medicinal chemistry point of view, an efficient method to fast synthesize diverse 4-substituted-2-quinolinones is still needed. Herein, we described an efficient method to synthesize 4-substituted-2-quinolinone-3-carboxylic acid ethyl esters in good yields. The key step of our approach involves substitution at 4-position of the quinolinone core using Suzuki and Sonogashira reactions.

RESULTS AND DISCUSSION

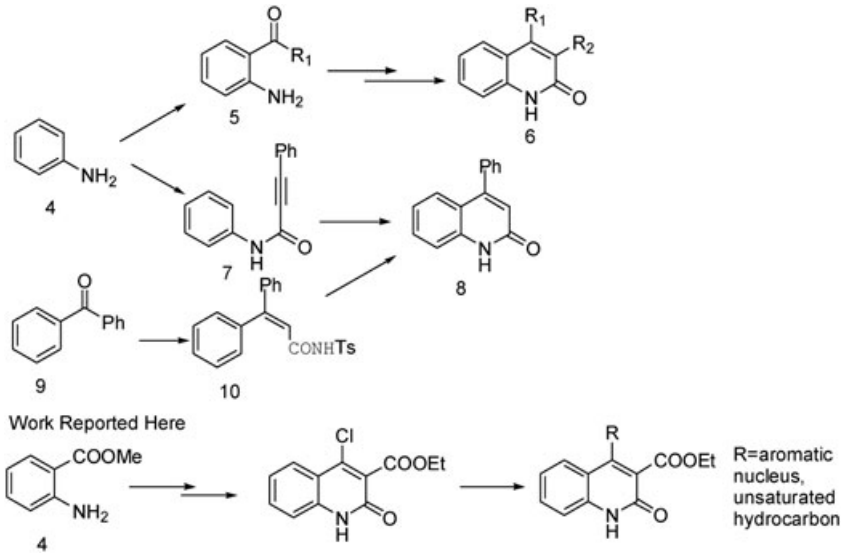
As shown in Scheme 3, the starting material **11** was initially reacted with ethyl malonyl chloride in the presence of triethylamine to give the intermediate amide. Without purification of the amide, the quinoline ring was formed to generate compound **12** by sodium hydride [6]. Then compound **12** was reacted with phosphoryl chloride to yield the dichloroquinoline **13**. Finally, compound **13** was dechlorinated in the presence of sodium acetate and acetic acid to provide the precursor compound **14** [7].

Because of the strong electron deficiency of 4-substituted quinolinones, compound **14** was considered as the substrate to perform Suzuki and Sonogashira reactions (Scheme 4). Several boric acids containing either electron-donating groups or electron-withdrawing groups, such as phenyl boric acid **15a**, 4-methoxy-phenyl boric acid **15b**, 3-cyano-phenyl boric acid **15c** and 2-allyl-4,4,5,5-tetramethyl-[1,3,2] dioxaborolane **15d** were selected to react with compound **14** in the presence of base under nitrogen for several hours. The reactions proceeded smoothly to produce the corresponding compounds **16a–d** in 77, 93, 71, 79% yield, respectively. Obviously, 4-methoxy-phenyl boric acid **15b** gave the highest yield (93%) compared with phenyl boric acid **15a** (77%) and 3-cyano-phenyl boric acid **15c** (71%), suggesting that the electron-donating group of phenyl ring had positive influence on the Suzuki reaction. Phenylacetylene **15e** and trimethylsilylacetylene **15f** were successfully introduced to 4-position of quinolinone ring by Sonogashira reaction in 88 and 56% yield, respectively.

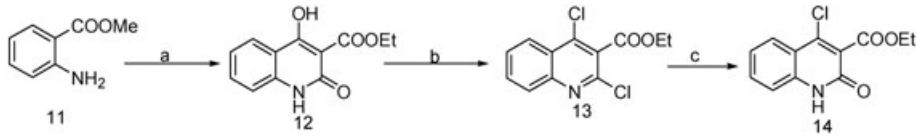
Scheme 1



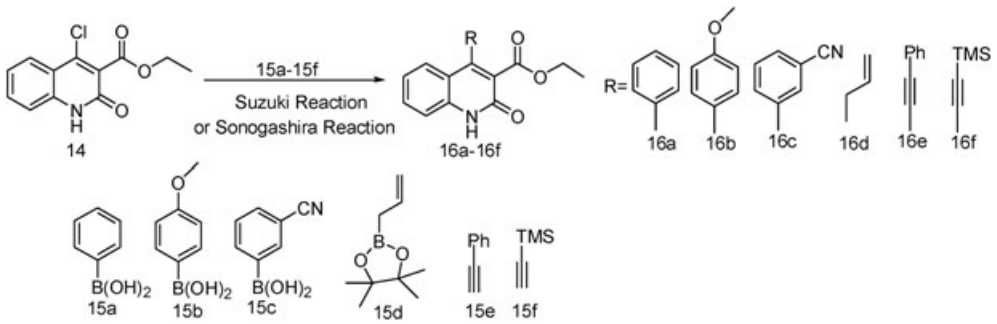
Scheme 2. The previous methods.



Scheme 3. Reagents and conditions: (a) monoethyl malonate, EDAC; NaH, ethanol. (b) POCl3, reflux. (c) sodium acetate, acetic acid.



Scheme 4



In conclusion, we successfully synthesized several 4-substituted quinolinones by Suzuki or Sonogashira reactions. The advantages of the method include high yields, operational simplicity, and suitability for medicinal chemistry of 4-substituted quinolinones and their derivatives.

EXPERIMENTAL

^{1}HNMR spectra were recorded on a Bruker DRX-500 (500 MHz). ^{13}CNMR spectra were obtained on a JNM-EX400 (100 MHz) and a Bruker DRX-500 (125 MHz). All reagents were used directly as obtained commercially, unless otherwise noted.

Typical procedure for 16a–d. A mixture of 4-chloro quinolinone **14** (100 mg, 0.4 mmol), K_2CO_3 (82 mg, 0.6 mmol), Pd $(PPh_3)_4$ (43 mg, 0.04 mmol), and the corresponding boric acid or boric acid ester **15a–d** (0.6 mmol) in 10 mL toluene and 1 mL water was refluxed at the atmosphere of nitrogen for 3–7 h, monitored by TLC, the solvents were evaporated *in vacuo* and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1:1).

2-Oxo-4-phenyl-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16a. ^{1}HNMR ($CDCl_3$): δ 0.96 (t, *J* = 6 Hz, 3H), 4.11 (m, 2H), 7.14 (t, *J* = 8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 1H), 7.39 (m, 3H), 7.48 (m, 3H), 7.54 (t, *J* = 8 Hz, 1H), 11.44 (s, 1H). ^{13}CNMR (125 MHz, $CDCl_3$): δ 13.68, 61.32, 116.80, 119.49, 122.91, 126.14, 127.59, 128.33, 128.78, 128.84, 131.53, 134.64, 138.41, 150.62, 161.09, 165.55. HRMS (EI): *m/z* Calcd. For $C_{18}H_{15}NO_3$: 293.1052, Found: 293.1054.

4-(4-Methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16b. ^{1}HNMR ($CDCl_3$): δ 1.04 (t, *J* = 6 Hz, 3H), 3.88 (s, 3H), 4.16 (m, 2H), 7.01 (d, *J* = 10 Hz, 2H), 7.14 (t, *J* = 7 Hz, 1H), 7.34 (m, 3H), 7.40 (d, *J* = 8 Hz, 1H), 7.53 (t, *J* = 7 Hz, 1H), 11.63 (s, 1H). ^{13}CNMR (125 MHz, $CDCl_3$): δ 13.85, 55.34, 61.31, 113.80, 116.66, 119.78, 122.81, 126.76, 127.63, 130.18, 131.40, 138.36, 160.05, 161.01, 165.77. HRMS (EI): *m/z* Calcd. For $C_{19}H_{17}NO_4$: 323.1158, Found: 323.1157.

4-(3-Cyanophenyl)-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16c. ^{1}HNMR ($CDCl_3$): δ 1.05 (t, *J* = 7 Hz, 3H), 4.16 (m, 2H), 7.12 (d, *J* = 7 Hz, 1H), 7.18 (t, *J* = 7 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.57 (t, *J* = 7 Hz, 1H), 7.64 (m, 2H), 7.71(s, 1H), 7.81 (m, 1H), 12.43 (s, 1H). ^{13}CNMR (125 MHz, $CDCl_3$): δ 13.81, 61.62, 112.86, 117.04, 117.95, 118.69, 123.35, 126.64, 126.85, 129.43, 132.05, 132.24, 132.50, 133.22, 135.96, 138.47, 147.84, 160.73, 164.90. HRMS (EI): *m/z* Calcd. For $C_{19}H_{14}N_2O_3$: 318.1004. Found: 318.1001.

4-Allyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16d. ^{1}HNMR ($CDCl_3$): δ 1.43 (m, 3H), 3.64 (d, *J* = 7 Hz, 2H), 4.46 (m, 2H), 5.17 (t, *J* = 10 Hz, 2H), 5.97 (m, 1H), 7.24 (d, *J* = 9 Hz, 1H), 7.28 (s, 1H), 7.53 (t, *J* = 7 Hz, 1H), 7.76 (d, *J* = 9 Hz, 1H), 10.63 (d, *J* = 5 Hz, 1H). ^{13}CNMR (125 MHz, $CDCl_3$): δ 14.23, 34.19, 61.70, 117.14, 117.96, 118.68, 122.88, 125.41, 126.52, 131.27, 133.63, 138.35, 147.36, 161.30, 166.35. HRMS (EI): *m/z* Calcd. For $C_{15}H_{15}NO_3$: 257.1052. Found: 257.1054.

2-Oxo-4-phenylethynyl-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16e. A mixture of 4-chloro quinolinone **14** (100 mg, 0.4 mmol), K_2CO_3 (82 mg, 0.6 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), PPh_3 (42 mg, 0.16 mmol), CuI (8 mg, 0.04 mmol) and phenylacetylene **15e** (61 mg, 0.6 mmol) in 10 mL acetonitrile was refluxed under nitrogen for 4 h, monitored by TLC, the solvent was evaporated in vacuo and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1:1).

^{1}HNMR ($CDCl_3$): δ 1.44 (t, *J* = 7 Hz, 3H), 4.52 (m, 2H), 7.34 (m, 2H), 7.44 (t, *J* = 7 Hz, 3H), 7.61 (m, 3H), 8.11 (d, *J* = 9 Hz, 1H), 11.39 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 14.33, 61.92, 82.14, 103.84, 111.89, 116.67, 118.72, 121.57, 123.33, 127.17, 128.64, 129.96, 132.01, 132.06, 132.49, 138.19, 160.64, 165.20. HRMS (EI): *m/z* Calcd. For $C_{20}H_{15}NO_3$: 317.1052. Found: 317.1052.

2-Oxo-4-trimethylsilanylethynyl-1,2-dihydroquinoline-3-carboxylic Acid Ethyl Ester 16f. A 25 mL sealed steel reactor was charged with a mixture of 4-chloro quinolinone **14** (200 mg, 0.8 mmol), K_2CO_3 (164 mg, 0.6 mmol), $Pd(OAc)_2$ (36 mg, 0.16 mmol), PPh_3 (170 mg, 0.64 mmol), CuI (30 mg, 0.16 mmol), trimethylsilylacetylene **15f** (23 mg, 2.4 mmol) in 25 mL toluene. The system was heated at 100 °C under nitrogen for 20 h, monitored by TLC, the solvent was evaporated in vacuo and the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1:3).

^{1}HNMR ($CDCl_3$): δ 0.32 (s, 3H), 1.45 (t, *J* = 5 Hz, 3H), 4.48 (m, 2H), 7.28 (t, *J* = 10 Hz, 1H), 7.37 (t, *J* = 7 Hz, 1H), 7.57 (m, 1H), 7.99 (d, *J* = 5 Hz, 1H), 11.97 (s, 1H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 0.00, 14.60, 62.28, 97.10, 111.48, 117.07, 119.06, 123.78, 127.57, 129.91, 130.10, 132.37, 138.55, 161.05, 165.40. HRMS (ESI): *m/z* Calcd. For $C_{17}H_{19}NNaO_3Si$ $[M + Na]^+$: 336.1026, Found: 336.1053.

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