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Transition metal-free one-pot synthesis of 2-substituted 3-carboxy-4-quinolone and chromone derivatives†

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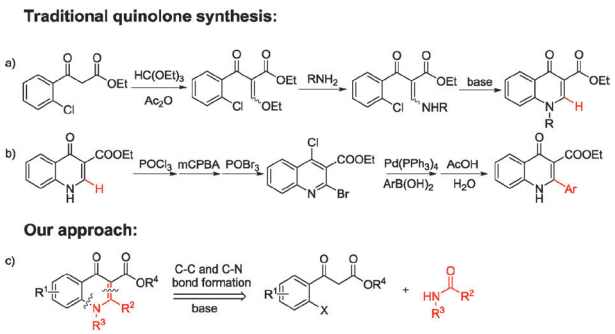
A novel one-pot synthesis of the 2-substituted 3-carboxy-4-quinolone/chromone derivatives from readily available 3-oxo-3-arylpropanoates and amides/acyl chlorides is reported, without any transition metal aid.

3-Carboxy-4-quinolones are among the most common scaffolds present in drugs and bioactive compounds.[1] Besides constituting an important category of marketed antibacterial agents (*e.g.*, Ciprofloxacin, Levofloxacin and Moxifloxacin), the 3-carboxy-4-quinolone derivatives have been found to exhibit a broad and potent spectrum of pharmacological activities, such as antitumor,[2] anxiolytic,[3] antiviral,[4] anti-HIV-1 integrase,[5] and cannabinoid receptor 2 agonist/antagonist activities.[6] All these make the scaffold a valuable synthetic target and continuously promote the efforts to develop new efficient synthetic strategies enabling rapid functionalization and diversification. Among these methods, the Grohe–Heitzer reaction[7] (Scheme 1a) and the Gould–Jacobs reaction[8] have been widely applied. However, it is still difficult to introduce a variable substituent at position 2 through those methods, presumably due to the steric hindrance of the carboxyl group at position 3. Few syntheses have been reported for 2-substituted 3-carboxy-4-quinolone derivatives with disadvantages of multi-steps (Scheme 1b),[9] rare substrates[10] or use of protecting groups.[11] The yields from these methods were usually low and thus limited their application in the preparation of derivatives. However, 2-substituted 4-quinolone derivatives have increasingly shown attractive biological activities, and the nature of 2-substituent specifies the biological profile.[12] Thus a convenient and efficient synthesis for this class of quinolones would warrant an extensive medicinal chemistry investigation and further drug development based on the drug-like scaffold.



Scheme 1 Strategies for the synthesis of 4-quinolone-3-carboxylates.

Herein, we design and develop a novel one-pot transition metal-free synthesis involving a tandem C–C bond and C–N bond formation to afford structurally diverse 2-substituted 3-carboxy-4-quinolone derivatives from 3-oxo-3-arylpropanoates and amides (Scheme 1c). Furthermore, when the amide is changed to the acyl chloride, this approach delivers 2-substituted 3-carboxy-4-chromone derivatives, which represent another versatile bioactive scaffold in drug discovery.[13] Distinct from traditional Buchwald–Hartwig amination[14] and Ullmann-type coupling reaction,[15] our methodology employed a base-promoted intramolecular N-arylation or O-arylation to achieve the annulation. To the best of our knowledge, this is the first synthesis of 2-substituted 3-carboxy-4-quinolone derivatives by a one-pot condensation using readily accessible amides and 3-oxo-3-arylpropanoates as starting materials, providing a simple and convenient alternative to the classical quinolone syntheses.

Based on the imine–enamine tautomerism, we envisioned that the condensation of halogen-substituted 3-oxo-3-arylpropanoate **1** and amide **2** would lead to the 2-substituted quinolone **4** *via* a tandem addition–elimination reaction (C–C coupling)/nucleophilic aromatic substitution reaction (C–N coupling) through an imine–enamine intermediate (**A** and **C**), as illustrated in Scheme 2. The competitive O-acylation (**B**) might occur. To accelerate the C–C coupling, the amide could be transformed into more reactive imidoyl chloride **3** by reacting with $SOCl_2$ *in situ*. Considering both couplings need base, we reasoned that the two-step reactions can be performed in one pot. Therefore, we chose K_2CO_3 as the base and DMF as the solvent to initiate the reaction. Because the fluoro group can serve as a handle to introduce further substituents and itself possesses a special nature in pharmacology, ethyl 3-oxo-3-(2,3,4,5-tetrafluorophenyl)propanoate (**1a**) and

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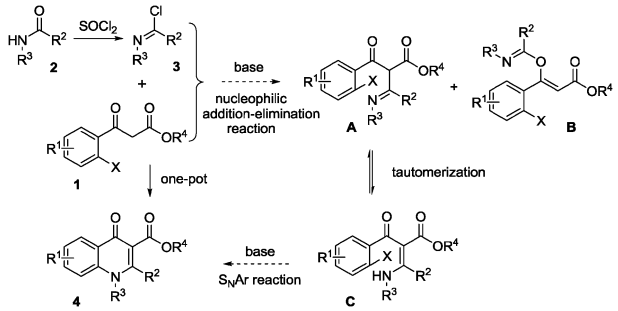


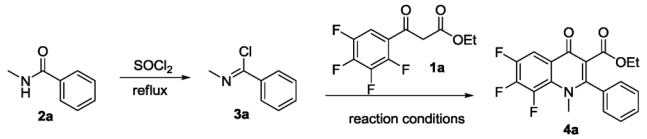
Scheme 2 One-pot synthesis design.

N-methylbenzamide (**2a**) were chosen as the model substrates to screen the base, solvent, and temperature in air for optimized reaction conditions.

The reaction mixture was first cooled to 0 °C for one hour to fulfil C–C coupling, then heated to 110 °C for another one hour to form the C–N bond. Gratifyingly, the reaction proceeded well, and the desired product **4a** was isolated in 68% yield (Table 1, entry 1). Adding organic base DIPEA to the reaction solution resulted in an increase in yield (entry 2, 74%), while the yield was lowered when only DIPEA was used as the base (entry 8, 51%). Hence the organic co-base was examined (entries 2–4), and DIPEA was proven to be the best. We further surveyed the inorganic bases (K_2CO_3, Na_2CO_3, Cs_2CO_3 and NaH), and found that the best yield was achieved when K_2CO_3 was used (entries 2, 5–7). The solvent was critical for this transformation. Use of other aprotic solvents such as toluene and DMSO caused a substantial drop in the yield (entries 9 and 10). Higher temperature was detrimental to the C–C coupling reaction (entries 11–13), owing to the increase of the undesired O-acylation by the competitive enolization of substrate **1a** at higher temperature. Overall, entry 2 stood out as the optimized set of conditions for this one-pot transformation.

With optimized conditions in hand, we turned to explore the reaction scope with respect to 3-oxo-3-arylpropanoate (Table 2, entries 1–13). A range of 3-oxo-3-arylpropanoates bearing electron-withdrawing groups such as trifluoromethyl, cyano, nitro and halogen

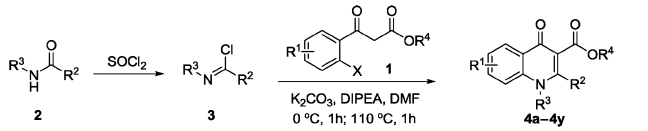
Table 1 Reaction conditions screening[a]



Entry	Solvent	Base1	Base2	T_1 [°C]	T_2 [°C]	Yield[b] [%]
1	DMF	K_2CO_3	—	0	110	68
2	DMF	K_2CO_3	DIPEA	0	110	74
3	DMF	K_2CO_3	Et_3N	0	110	38
4	DMF	K_2CO_3	Pyridine	0	110	19
5	DMF	Na_2CO_3	DIPEA	0	110	43
6	DMF	Cs_2CO_3	DIPEA	0	110	58
7	DMF	NaH	DIPEA	0	110	7
8[c]	DMF	—	DIPEA	0	110	51
9	PhMe	K_2CO_3	DIPEA	0	110	23
10	DMSO	K_2CO_3	DIPEA	0	110	11
11	DMF	K_2CO_3	DIPEA	40	110	71
12	DMF	K_2CO_3	DIPEA	80	110	67
13	DMF	K_2CO_3	DIPEA	110	110	32

[a] Reaction conditions: **1a** (2 mmol), **2a** (2.4 mmol), $SOCl_2$ (12 mmol), base1 (6 mmol), base2 (4 mmol), solvent (10 mL), T_1, T_2 both for 1 h, in air. [b] Values are the overall yields of isolated products. [c] Base2 (16 mmol).

Table 2 The substrate scope of the one-pot synthesis of 2-substituted-4-quinolone derivatives[a,b]



Entry	Product	Yield[c] (%)
1	**4a**: R^1 = 6,7,8-tri-F	74
2	**4b**: R^1 = 6-I,7-F	74
3	**4c**: R^1 = 6-I,7-F	64
4	**4d**: R^1 = 7-F	65
5	**4e**: R^1 = 7-NO_2	85
6	**4f**: R^1 = 6-CF_3	73
7	**4g**: R^1 = 7-CN	68
8	**4h**: R^1 = 6-Me	43
9	**4i**: R^1 = 7-OMe	48
10	**4j**: R^1 = H, X = F	50
11	**4j**: R^1 = H, X = Cl	10
12	**4j**: R^1 = H, X = Br	41
13	**4j**: R^1 = H, X = I	11
14	**4k**: R^2 = 4-OMe-Ph	70
15	**4l**: R^2 = 4-F-Ph	66
16	**4m**: R^2 = 4-Cl-Ph	71
17	**4n**: R^2 = 2-I-Ph	77
18	**4o**: R^2 = 2,6-di-Cl-Ph	74
19	**4p**: R^2 = 3-CF_3-Ph	72
20	**4q**: R^2 = 4-NO_2-Ph	65
21	**4r**: R^2 = 2-NO_2-Ph	81
22	**4s**: R^2 = 2-furanyl	41
23	**4t**: R^3 = cyclopropyl	56
24	**4u**: R^3 = isopropyl	77
25	**4v**: R^3 = allyl	64
26	**4w**: R^3 = *n*-butyl	75
27	**4x**: R^3 = benzyl	63
28[d]	**4y**: R^3 = cyclohexyl	85

[a] Reaction conditions: **1** (2 mmol), **2** (2.4 mmol), $SOCl_2$ (12 mmol), K_2CO_3 (6 mmol), DIPEA (4 mmol), DMF (10 mL), under air. [b] X = F unless otherwise specified. [c] Values are the overall yields of isolated products. [d] Reaction conditions: 120 °C, 6 h for the C–N coupling step.

group substituted on the aromatic ring were all competent nucleophiles in the coupling reaction with imidoyl chloride **3** and subsequent cyclization to give the corresponding products in good yields (entries 1–7). Significantly, compound **4e** was successfully isolated in 85% overall yield for all three steps (entry 5). However, the electron-donating group (*i.e.* methyl or methoxy) substituted on the aromatic ring disfavored the condensation with a marked decrease in the yield (entries 8 and 9, 43% and 48% yield, respectively). These results indicated that the electronic effect of the substituent played an important role in the last nucleophilic aromatic substitution step (C–N bond formation). The electron-withdrawing group significantly promoted the transformation, whereas the electron-donating group exerted an adverse effect. It was also observed that ethyl propanoate **1b** was more reactive than the methyl propanoate counterpart **1c** with a 10% increase in the yield. We further examined the reactivity of the halogen substituent on the aryl ring involved in the N-arylation reaction. Among the four halogens, fluoro was the most suitable and bromo was the second, but chloro and iodo only gave the corresponding products in much lower yields (entries 10–13).

To further evaluate the scope of the reaction, a survey of amide substrates was conducted (Table 2, entries 14–28). We changed the R^2 group of the amide first. A range of variously substituted phenyl rings were well tolerated to furnish the quinolone products in moderate to good yields (entries 14–22). An interesting steric hindrance effect was observed in this reaction, with the yields being increased as the steric hindrance of R^2 increased (entries 17, 18, and 21 *vs.* entries 16, 19, and 20). Not surprisingly, only 41% yield was obtained with *N*-methylfuran-2-carboxamide as the starting material (entry 22), because of the low yield of the corresponding imidoyl chloride and relatively less steric hindrance. Attempts to further expand the scope to aliphatic amides were unfruitful, mainly due to the presence of the α-hydrogen which complicated the formation of the precursor imidoyl chloride. Finally, we examined the R^3 substituent on the amide (entries 23–28). All substrates bearing an aliphatic or aromatic group afforded products in good yields. Similar to the R^2 group, the steric hindrance favored the formation of the desired products. Notably, **4y** was isolated in an overall yield of 85% for all three steps (entry 28), but its C–N bond forming step required higher temperature and longer reaction time, up to 120 °C for 5 hours. Further transformation of these quinolone carboxylates is widely feasible, *e.g.*, N-debenzylation of compound **4x** by hydrogenation readily afforded 4(1*H*)-quinolone **4z** (see ESI†).

Having established a robust synthesis of a diverse array of 2-substituted-4-quinolone-3-carboxylates, we were interested in whether the approach could be extended to chromone synthesis by switching N-arylation to O-arylation, namely, using a hydroxyl as the nucleophile. To our delight, when the imidoyl chloride was changed to acyl chloride, a variety of 2-substituted-3-carboxy-4-chromones were generated in good yields (Table 3). Similar to the synthesis of the quinolone, the yields increased as the steric hindrance of aryl chloride increased. But the electronic effect seemed to be slight. In general, aromatic acyl chloride performed better than aliphatic acyl chloride, thus providing higher yields.

In conclusion, we have developed a convenient, practical, and highly efficient method for the synthesis of 2-substituted-3-carboxy quinolone and chromone derivatives. The one-pot synthesis uses readily available 3-oxo-3-arylpropanoates and amides/acyl chlorides as the starting materials, inexpensive DIPEA and K_2CO_3 as the base, and DMF as the solvent, eligible to a broad substrate scope. Since the current modifications at position 2 are rather limited for the 3-carboxy-4-quinolone and chromone, this simple and versatile methodology will be an excellent complement for the classical methods.

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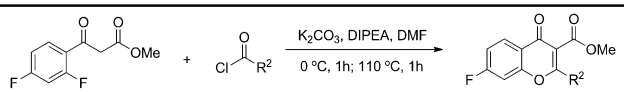
Table 3 The substrate scope of the one-pot synthesis of 2-substituted-3-carboxy-chromone derivatives[a]



Entry	Product	Yield[b] (%)
1	**6a**: R^2 = Ph	64
2	**6b**: R^2 = 4-Me-Ph	61
3	**6c**: R^2 = 4-F-Ph	69
4	**6d**: R^2 = 2-Cl-Ph	73
5	**6e**: R^2 = 2,3-di-OMe-Ph	61
6	**6f**: R^2 = 3-NO_2-Ph	50
7	**6g**: R^2 = 2-furanyl	63
8	**6h**: R^2 = Me	36
9	**6i**: R^2 = cyclobutyl	43

[a] Reaction conditions: **1d** (2 mmol), **5** (2.4 mmol), $SOCl_2$ (12 mmol), K_2CO_3 (6 mmol), DIPEA (4 mmol), DMF (10 mL), in air. [b] Values are the overall yields of isolated products.

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