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An efficient route from coumarins to highly functionalized *N*-phenyl-2-quinolinones via Buchwald–Hartwig amination

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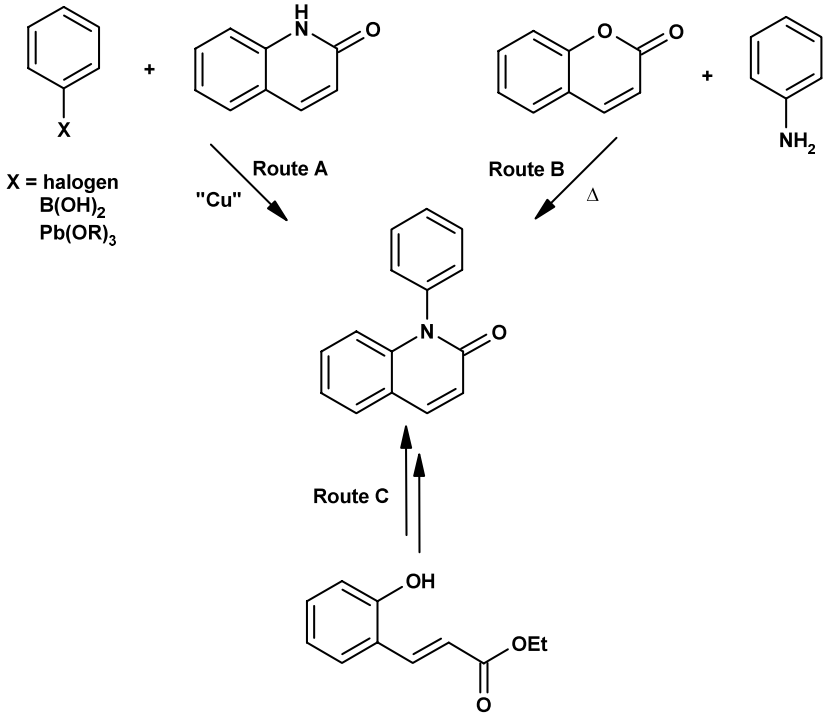
Abstract—Multiple substituted *N*-phenyl-2-quinolinones were obtained in a convenient four-step route from a variety of commercially available coumarins, utilizing customised Buchwald–Hartwig amination protocols for the key reaction. Whereas simple aminolysis of coumarins is limited to non-electron-deficient, sterically unhindered derivatives of aniline under harsh conditions, the present method allows for conversions with multiple substituted aromatic amines, as demonstrated by the example of chlorinated aminosalicylates.

Substituted *N*-phenyl-2-quinolinones represent the structural basis of many biologically active compounds, such as protein kinase inhibitors, immunomodulators, anti-ulcer agents, hypoglycemics, farnesyl transferase inhibitors, and antiviral agents.[1a–f] We had specific interest in the substance class for the evaluation of potential immunosuppressors and sought a synthetic route that would introduce as much structural diversity as possible, with a focus on salicylic acid derivatives as the *N*-phenyl moiety, and variability of the quinolinyl substitution pattern.

Known procedures for the synthesis of *N*-phenyl-2-quinolinones (Scheme 1) report the coupling of *nor-*



Scheme 1.

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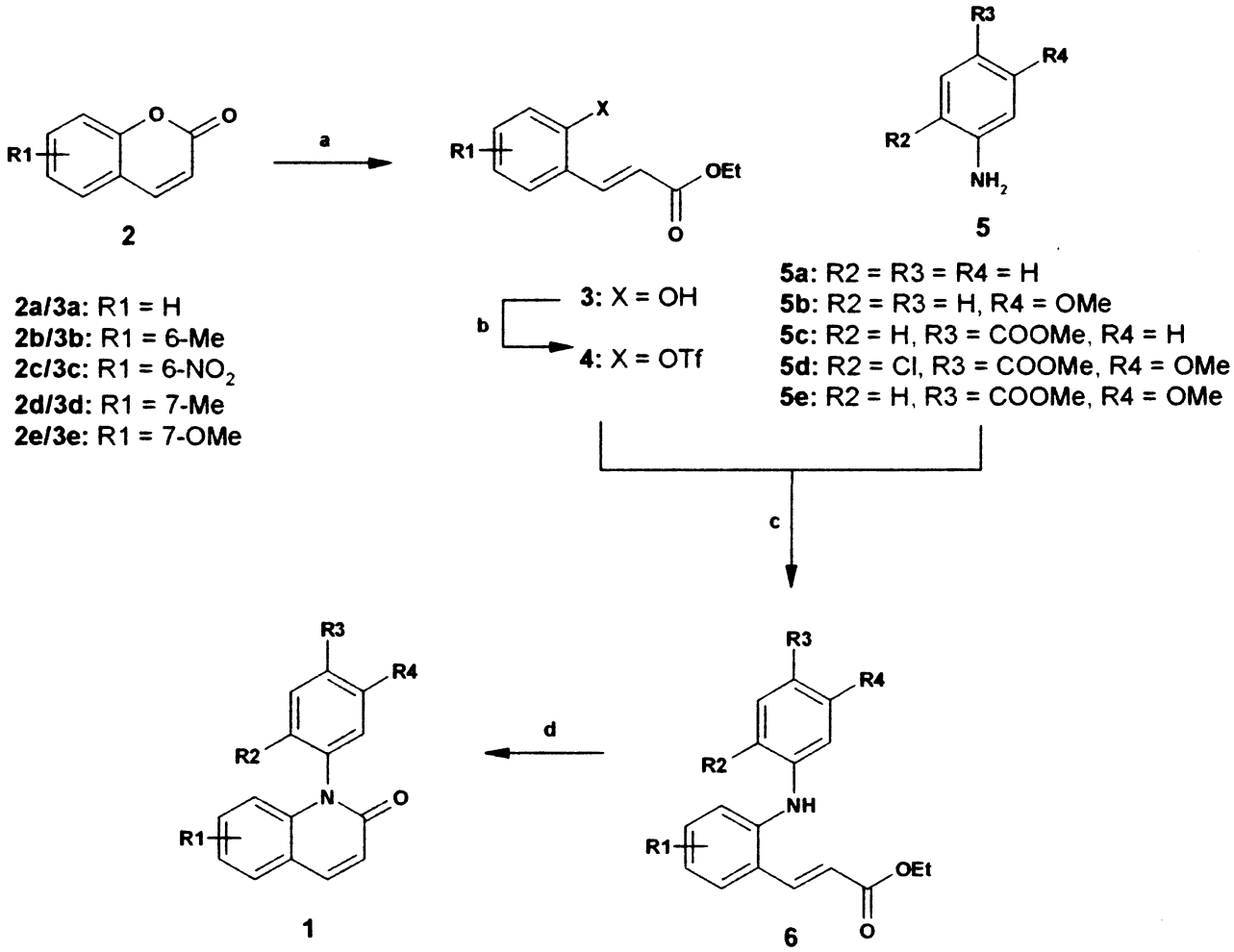


Scheme 2. *Reagents and conditions*: (a) NaOEt, EtOH, reflux, 4 h; (b) Tf_2O, Et_3N, CH_2Cl_2, rt, 2 h; (c) see Table 1; (d) NaOMe, MeOH, reflux, 1–4 h (see also Table 2).

quinolinones with aryl halides,[2] boronic acids,[3] or organolead reagents[4] in the presence of copper catalysts (*Route A*). Few examples were given where coumarins were directly aminolyzed upon treatment with substituted anilines[5] (*Route B*). Both of these methods bear significant limitations. *Route A* is certainly compromised by the low number of commercially available, functionalized 2-quinolinones, and structurally diverse boronic acids or organolead reagents are either expensive or hazardous, or have to be synthesized in a lengthy process. Aryl halides do not necessarily fall under these limitations but give very poor yields in this type of coupling reactions. When applying *Route B* in

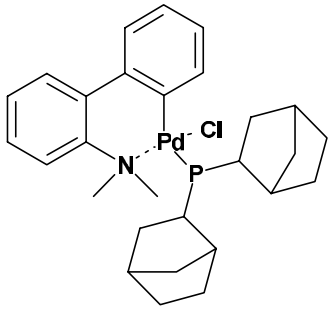
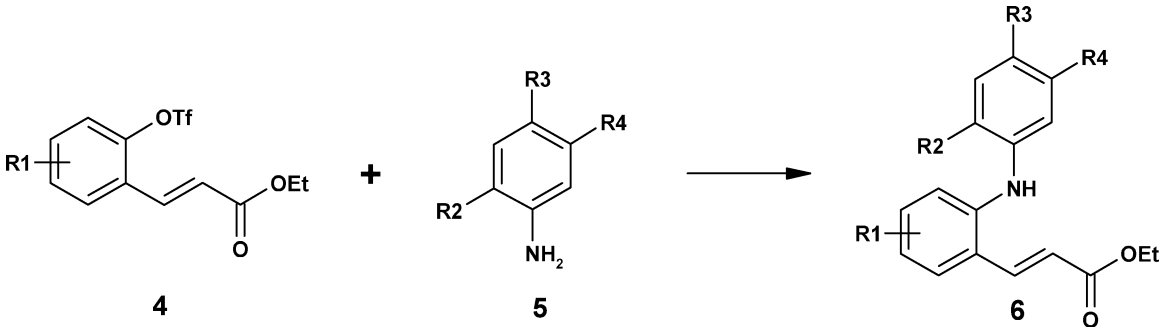


Figure 1. SK-CC01-A.

Table 1. Buchwald–Hartwig amination



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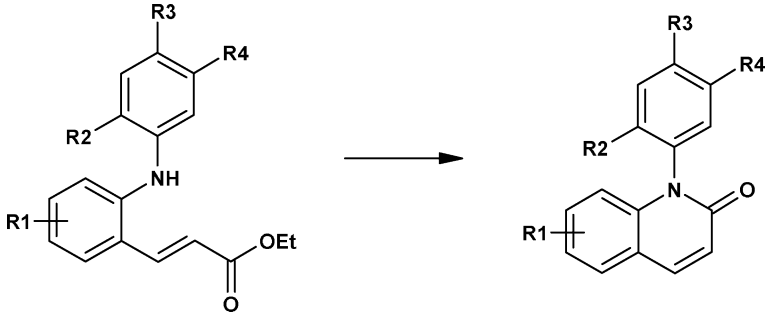
Entry	R1	R2	R3	R4	Prod.	M[a]	Time (h)	Yield (%)
4a/**5a**	H	H	H	H	**6a**	A	20	73
4a/**5b**	H	H	H	OMe	**6b**	A	20	79
4a/**5c**	H	H	CO_2Me	H	**6c**	A	24	60
4b/**5d**	6-Me	Cl	CO_2Me	OMe	**6d**	A	24	45
						B	24	80
						C	0.3	47
4c/**5d**	6-NO_2	Cl	CO_2Me	OMe	**6e**	A	24	42
						B	24	77
						C	0.3	38
4d/**5e**	7-Me	H	CO_2Me	OMe	**6f**	A	24	73
4d/**5d**	7-Me	Cl	CO_2Me	OMe	**6g**	A	24	48
4e/**5d**	7-OMe	Cl	CO_2Me	OMe	**6h**	A	24	51

[a] Methods: A, $Pd_2(dba)_3$ (25 mol%), (±)-BINAP, Cs_2CO_3, toluene, reflux; B, SK-CC01-A (5 mol%), Cs_2CO_3, toluene, reflux; C, $Pd_2(dba)_3$ (25 mol%), (±)-BINAP, Cs_2CO_3, acetonitrile, 150°C, microwave irradiation.

Table 2. Cyclization of aminoesters



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Entry	R1	R2	R3	R4	Pr.	Time (h)	Yield (%)
6a	H	H	H	H	**1a**	4	72
6b	H	H	H	OMe	**1b**	3	64
6c	H	H	CO_2Me	H	**1c**	3	67
6d	6-Me	Cl	CO_2Me	OMe	**1d**	3	50
6e	6-NO_2	Cl	CO_2Me	OMe	**1e**	1	84
6f	7-Me	H	CO_2Me	OMe	**1f**	4	64
6g	7-Me	Cl	CO_2Me	OMe	**1g**	4	63
6h	7-OMe	Cl	CO_2Me	OMe	**1h**	4	43

our laboratory, we observed that aminolysis of coumarin did not take place with anilines featuring electron-withdrawing groups in the *para* position or any *ortho*-substituents for sterical reasons, both crucial structural features in our series.

Furthermore, *Route B* usually requires harsh conditions (extensive reflux in high-boiling solvents) to overcome the pronounced sluggishness of the reactions; a number of functional or protective groups necessary for diversity would not tolerate such conditions. For these rea-

sons we sought an alternative route that would be accomplished in only few synthetic steps from a variety of cheap starting materials, providing good yields while tolerating a large variety of functional groups. A promising pathway (*Route C*) was envisaged considering the ease at which diarylamines can be synthesized under Buchwald–Hartwig conditions.[6] Providing a useful synthon for amination, bearing a carboxyl side chain for final stage cyclization, we opted for triflated *o*-hydroxycinnamates that would be readily available from coumarins.

The presented synthetic route is primarily based on a Buchwald–Hartwig palladium-catalyzed aryl-amino coupling reaction between triflates of the general formula **4** and anilines of the general formula **5** (Scheme 2). Triflates **4** were obtained by ethanolysis of commercially available coumarins **2**[7] and subsequent sulfonylation of *o*-hydroxycinnamates **3**. ^{1}H NMR analysis indicated that the double bond conformation in **3** was exclusively (*E*). The Buchwald–Hartwig amination was in general performed following a literature protocol,[8] using $Pd_2(dba)_3$ as catalyst (4 mol%) and (±)-BINAP as ligand in the presence of Cs_2CO_3 and toluene (reflux). Although these conditions reportedly give good to excellent yields for many substrates, and we ourselves obtained yields of 60–80% for *meta*- and/or *para*-substituted anilines after 24 h, we observed a significant decrease of the conversion rate when employing the sterically hindered aniline **5d** (R2 = Cl).[9] Products **6d**, **6e**, **6g** and **6h** could not be afforded in more than 50% yield even after prolonged heating and addition of fresh catalyst. We therefore investigated this particular reaction with a new catalyst that has been recently described as a very valuable tool in C–C and C–N coupling reactions, [bis(bicyclo-[2.2.1]hept-2-yl)phosphine]chloro[2′-(dimethylamino-κN)-[1,1′-biphenyl]-2-yl-κC]palladium (SK-CC01-A) (Fig. 1).[10] The reaction proceeded with a faster rate to yield 80% of **6d** and **6e**, respectively, after 24 h, using 4 mol% of catalyst. When applied to other substrates, SK-CC01-A could not elevate yields up to more than 80% but shortened the required reaction time for this conversion to some extent.

Another improvement, although limited to the small loading capacity of the used equipment, was offered by conducting the Buchwald amination under microwave irradiation, as described for aryl bromides by Wan et al.[11] Thus, upon replacement of toluene with acetonitrile, similar yields as achieved with conventional synthesis were obtained after only 15 min at 150°C,[12] which underlines the striking superiority of microwave-assisted technology for small-scale procedures in the field of palladium-catalyzed coupling reactions. An overview of all substrates and reaction conditions of Buchwald–Hartwig amination reactions is presented in Table 1.

In the final step, aminoesters **6a**–**h** underwent base-triggered cyclization, taking advantage of the relative acidity of the secondary amine hydrogen. Simple treatment with NaOMe/MeOH afforded products **1a**–**h** in moderate to good yields.[13] It was evident that the electronic nature of both aromatic rings had a significant impact

Table 3. Analytical data for **1b**–**h**

Compd.	^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm)	^{13}C NMR (400 MHz; $CDCl_3$) δ (ppm)	HR-MS m/z
1b	7.79 (d, 1H, 9.5), 7.59 (dd, 1H, 7.7, 1.4), 7.51 (t, 1H, 8.1), 7.35 (td, 1H, 8.2, 1.5), 7.20 (td, 1H, 8.2, 0.8), 7.07 (dd, 1H, 2.4, 8.4), 6.88 (m, 1H), 6.82 (t, 1H, 2.3), 6.79 (d, 1H, 9.5), 6.70 (d, 1H, 8.5), 3.83 (s, 3H)	162.2, 161.1, 141.1, 139.8, 138.7, 130.9, 130.2, 128.2, 122.3, 122.2, 120.8, 120.3, 116.0, 115.0, 114.1, 55.4	252.1 $(M+H)^+$
1c	8.3 (d, 2H, 7.3), 7.80 (d, 1H, 9.6), 7.6 (dd, 1H, 7.5, 1.3), 7.40 (d, 2H, 7.3), 7.35 (td, 1H, 4.1, 1.7), 7.22 (t, 1H, 7), 6.80 (d, 1H, 9.6), 6.60 (d, 1H, 8.5), 4.0 (s, 3H)	166.6, 162.4, 142.2, 141.1, 140.5, 132.0, 131.2, 130.8, 129.6, 128.9, 123.0, 122.5, 120.7, 116.0	280.1 $(M+H)^+$
1d	8.06 (s, 1H), 7.77 (d, 1H, 9.6), 7.42 (s, 1H), 7.20 (dd, 1H, 7.6, 2.0), 6.95 (s, 1H), 6.76 (d, 1H, 9.6), 6.46 (d, 1H, 8.60), 3.94 (s, 3H), 3.87 (s, 3H), 2.41 (s, 3H)	164.9, 161.2, 158.9, 140.3, 139.4, 137.6, 133.5, 132.6, 131.9, 128.4, 124.3, 122.1, 121.9, 120.2, 114.8, 114.4, 56.6, 52.5, 20.6	358.1 $(M+H)^+$
1e	8.57 (d, 1H, 2.5) 8.25 (dd, 1H, 9.2, 2.5), 8.11 (s, 1H), 7.95 (d, 1H, 9.5), 6.98 (s, 1H), 6.94 (d, 1H, 9.5), 6.71 (d, 1H, 9.2), 4.0 (s, 3H), 3.9 (s, 3H)	165.0, 164.2, 161.1, 159.4, 143.9, 140.2, 138.5, 134.1, 125.7, 124.9, 124.6, 124.3, 123.3, 120.2, 116.1, 114.5, 57.1, 53.0	389.1 $(M+H)^+$
1f	8.02 (d, 1H, 8.2), 7.75 (d, 1H, 8.5), 7.48 (d, 1H, 7.9), 7.04 (dd, 1H, 7.9, 1.4), 6.96–6.88 (m, 2H), 6.70 (d, 1H, 9.5), 6.43 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 2.41 (s, 3H)	166.5, 162.5, 160.9, 142.8, 141.7, 141.2, 140.3, 133.7, 128.6, 124.4, 121.3, 121.1, 121.0, 118.5, 116.1, 113.3, 56.6, 52.6, 22.4	324.1 $(M+H)^+$
1g	8.06 (s, 1H), 7.77 (d, 1H, 9.6), 7.50 (d, 1H, 8.0), 7.05 (dd, 1H, 8.0, 1.4), 6.94 (s, 1H), 6.70 (d, 1H, 9.6), 6.31 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 2.32 (s, 2H)	165.3, 161.8, 159.3, 142.1, 140.7, 140.2, 139.9, 133.8, 128.9, 124.8, 124.7, 122.7, 121.1, 118.5, 115.3, 114.9, 57.0, 52.8, 22.4	358.1 $(M+H)^+$
1h	8.1 (s, 1H), 7.75 (d, 1H, 10.5), 7.55 (d, 1H, 8.6), 6.95 (s, 1H), 6.85 (dd, 1H, 6.3, 2.3), 6.61 (d, 1H, 12.5), 6.0 (d, 1H, 2.3), 3.95 (s, 3H), 3.9 (s, 3H), 3.7 (s, 3H)	165.2, 162.3, 162.1, 159.4, 141.7, 140.7, 139.8, 134.0, 130.4, 124.6, 122.5, 119.1, 114.9, 114.8, 110.6, 99.9, 57.0, 55.9, 52.9	374.1 $(M+H)^+$

on the conversion rate and the yield after several hours of reflux. A reaction period longer than indicated was considered disadvantageous due to decomposition (TLC), also the reason for which no quantitative conversions were observed. With both R1 and R3 being electron-withdrawing groups, such as $-NO_2$ and –COOMe (**1e**), located in the para position of the amino substituent, the promoted acidity enhanced the rate as compared to 'neutral' or electron-donating groups. This manifested in a time/yield profile as demonstrated in Table 2. Analytical data for **1b**–**h** are presented in Table 3. **1a** Has been synthesized via *Route A* and thoroughly characterized by Wawzonek et al.[2]

In conclusion, we have discovered an efficient and convenient route to convert commercial coumarins into multiple substituted *N*-phenyl-2-quinolinones without the limitations usually observed in this process. A great potential of time and yield optimization was offered by the choice of catalyst and microwave irradiation in the key step of the pathway. The present work should be easily reproducible with other amine substrates, including heterocyclic scaffolds, with a good chance of being broadly applied.

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12. A representative procedure is described: A mixture of **4c** (100 mg, 0.27 mmol), **5d**[7] (76 mg, 0.35 mmol), cesium carbonate (135 mg, 0.41 mmol), $Pd_2(dba)_3$ (7.8 mg, 0.008 mmol), BINAP (7.8 mg, 0.012 mmol) and HPLC grade acetonitrile (2 mL) is placed in a 5mL high-pressure glass vial and reacted in an Emrys™ microwave optimizer (150°C, 15 min). After cooling, the mixture was poured on 1N HCl (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers are washed with brine (1×20 mL), dried (Na_2SO_4/charcoal) and evaporated. The residue is purified by flash chromatography (appr. 10 g of silica gel, eluent: toluene/EtOAc = 3:1) to yield 73 mg (84%) of **6e**. TLC: toluene/EtOAc = 3:1 (R_f = 0.5).
13. A representative procedure is described: **6g** (4.11 g, 10.2 mmol) and NaOMe (1.11 g, 20.4 mmol) are dissolved in anhydrous MeOH (100 mL) and refluxed in an argon atmosphere for 4 h. After cooling, the mixture is poured on 1N HCl (200 mL) and extracted with EtOAc (2×200 mL). The combined organic layers are washed with brine (2×200 mL), dried (Na_2SO_4) and evaporated. The residue is purified by flash chromatography (appr. 100 g of silica gel, eluent: toluene/EtOAc = 1:1) to yield 2.14 g (63%) of **1g**. TLC: toluene/EtOAc = 1:1 (R_f = 0.2).