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Synthetic Methods

A Mild and Regioselective Route to Functionalized Quinazolines

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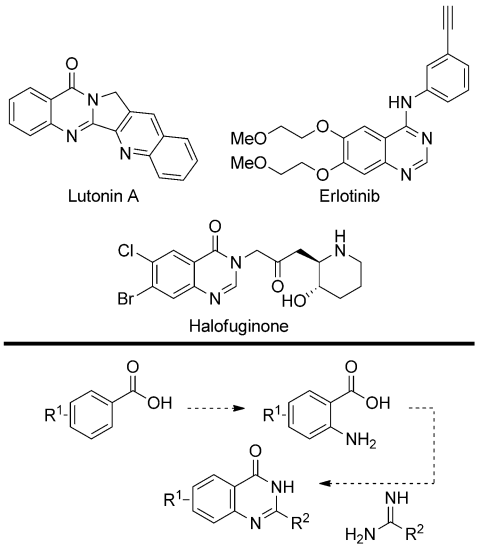
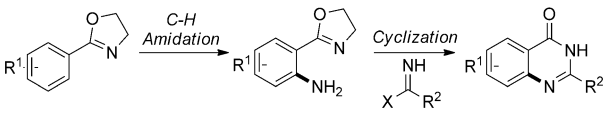
Abstract: A Rh-catalyzed *ortho*-amidation cyclocondensation sequence gave a range of 4-aminoquinazolines in high yield. The method features a remarkably mild C(sp^2)–H activation step and can be exploited to rapidly access compounds with established biological activity.

Quinazolines and quinazolinones represent important classes of heteroaromatic compounds, and they are found as core motifs in many natural products and drug candidates, such as luotonin A, erlotinib and halofuginone (Scheme 1).[1] Traditional approaches to these compounds typically involve the elaboration of *ortho*-disubstituted aromatic precursors, such as anthranilic acid derivatives, which are either used directly or are generated in situ.[2] However, a limited number of appropriate 1,2-disubstituted precursors are commercially available, and the preparation of these intermediates requires appropriately positioned activating groups, as well as adding further steps to the synthetic sequence. In contrast, benzoic acids represent a rich source of commercial aromatic precursors, and we became interested in exploiting these compounds for the synthesis of quinazoline derivatives. Specifically, these readily available starting materials seemed to be ideally suited to generating a broad variety of quinazolinone derivatives through a multicomponent coupling strategy constituting an *ortho*-amidation/condensation sequence.



Scheme 1. Direct amidation strategy to quinazolinones.

With respect to the *ortho*-amidation step, recent developments in C(sp^2)–H amidation appeared to offer a particularly convenient approach to the required 1,2-disubstituted benzene derivatives.[3,4] Indeed, Yu and co-workers have reported an elegant Rh-catalyzed amidation that provides anthranilic acids from the corresponding *N*-chloroamines, although this method generally requires the presence of substituents *ortho* to the carboxylic acid to avoid diamidation.[5] To control the amidation step and thereby establish a general method of quinazoline synthesis with a broad range of substitution patterns, we were attracted to the use of an oxazoline, because it appeared to offer the best opportunity of directing *ortho*-amidation while representing latent carboxylic acid functionality for conversion to the desired heterocycles. In addition, our preference for the chosen directing group was increased by the ability of an oxazoline to be easily prepared from carboxylic acids by Appel methodology,[6] from nitriles by the Witte–Seeliger reaction,[7] or from aldehydes by the synthesis of oxazolidines,[8] further broadening the range of commercially available starting materials for our synthetic strategy. Oxazolines have been relatively rarely used in C(sp^2)–H amidation, although Chang and Su have reported a small number of examples using sulfonyl azides or acyloxy carbamates,[9] and sulfonamides[10] under Ir and Rh catalysis, respectively. Therefore, we decided to investigate the scope of oxazoline directed C(sp^2)–H amidation with a view to exploiting this motif as a key component in a subsequent condensation reaction to quinazolines and quinazolinones (Scheme 2). The synthetic manipulation of directing groups after they have been used in C–H activation is a potentially powerful strategy, but one that has been relatively rarely utilized to date.[11]



Scheme 2. Proposed synthetic strategy.

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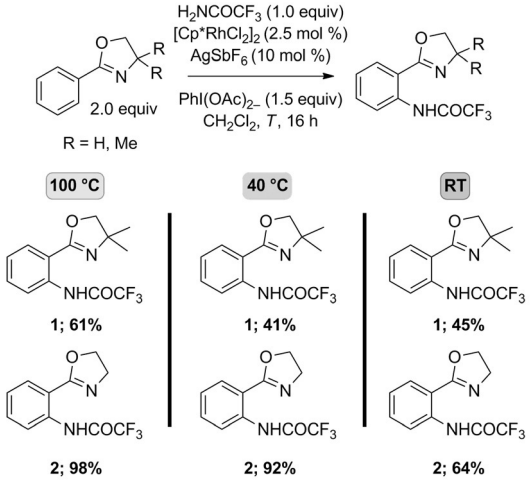
Because the employment of oxazoline directing groups for *ortho*-amidation was relatively under-developed, we began our studies by this process. Su and co-workers reported that oxazolines promote the incorporation of sulfonamides under Rh catalysis;[10] however, we decided to focus our attention on the use of the less reported trifluoroacetamide, because we believed that this amide source would make the subsequent transformation to the desired heterocycles more straightforward. We began by investigating a small series of oxazolines, and as shown in Scheme 3, we were surprised to find that the

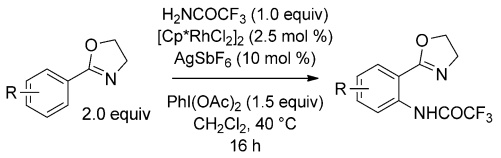


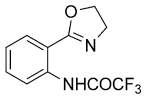
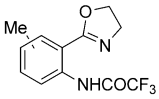
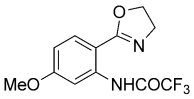
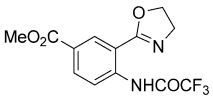
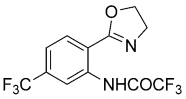
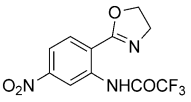
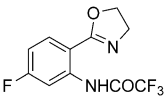
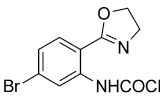
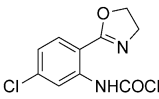
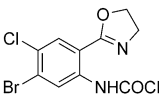
Scheme 3. Optimisation of C–H amidation.

efficiency of the amidation reaction was affected by the degree of substitution at C-4 of the oxazoline ring. We concluded that the unsubstituted oxazoline would be the most effective directing group for the *ortho*-amidation step. In addition, we were even more surprised to find that the temperature of the reaction could be decreased from 100 °C to room temperature with only a moderate decrease in reaction yield over a time period of 16 h. Contrary to Su's report, in which the elevated temperature of 100 °C is required to promote reaction between the oxazoline substrate and the sulfonamide source,[10] we found that an optimal temperature of 40 °C gave smooth amidation leading to the desired product **2** in an isolated yield of 92%.[12]

Next, we decided to investigate the scope of the amidation with respect to the aromatic ring. The requisite 2-aryloxazoline substrates were readily prepared in a one-pot procedure from commercial carboxylic acids.[13] As depicted in Table 1, a wide range of functionalities were well tolerated by the amidation reaction, providing the desired mono-aminated products only in yields of 72–100%. In general, amidation proceeded at the most sterically accessible position on the aryl ring. Moreover, a range of substitution patterns were compatible; *ortho*-, *meta*- and *para*-Me arenes underwent amidation in high yield and with excellent regiocontrol (entries 2–4). Both electron-withdrawing and -donating substituents were also tolerated with ester, nitro, trifluoromethyl and methoxy-substituted benzene derivatives affording products in excellent yield (entries 5–8). Finally, substrates bearing a series of halides were also very effective. For example, we prepared **13**, which is a precursor to the halofuginone quinazolinone. Notably, the documented synthesis of this particular heterocycle requires a linear sequence of four steps.[14] Finally, we were able to successfully conduct larger scale reactions using reflux apparatus instead of sealed Schlenk tubes (see entries 1, 12). Moreover, lowering the catalyst loading to 1 mol% gave **2** with only a small drop in yield.

Table 1. Scope of the C–H amidation.

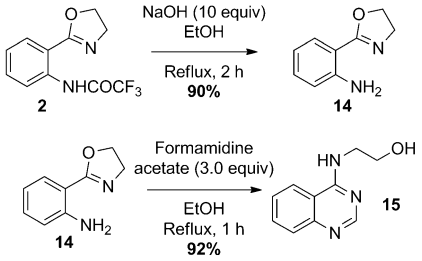


Entry[a]	Product	Yield [%][b]
1		**2**; 92(94)[c](76)[d]
2		4-Me; **3**; 84
3		3-Me; **4**; 72
4		2-Me; **5**; 74
5		**6**; 100
6		**7**; 77
7		**8**; 100
8		**9**; 100
9		**10**; 97
10		**11**; 96
11		**12**; 92
12		**13**; 72(76)[e]

[a] Reaction conditions: oxazoline substrate (0.4 mmol), trifluoroacetamide (0.2 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $PhI(OAc)_2$ (0.3 mmol), dichloromethane (2.0 mL), 40 °C, 16 h. [b] Isolated yield. [c] Reaction performed on a 4.42 mmol scale with $[RhCp^*Cl_2]_2$ (2.5 mol%) and $AgSbF_6$ (10 mol%). [d] Reaction performed on a 4.42 mmol scale with $[RhCp^*Cl_2]_2$ (1.0 mol%) and $AgSbF_6$ (4.0 mol%). [e] Reaction performed on a 1.0 mmol scale with $[RhCp^*Cl_2]_2$ (2.5 mol%) and $AgSbF_6$ (10 mol%).

With *ortho*-amido 2-aryloxazolines in hand, we began exploration of the final condensation step towards quinazoline derivatives. Initial attempts to directly condense trifluoroacetamides with formamide in the presence of acid led only to complex reaction mixtures and product decomposition.

Gratifyingly, hydrolysis of **2** led to the corresponding aniline **14** in an excellent yield of 90%, and subsequent condensation with formamidine acetate resulted in efficient cyclization to generate 4-aminoquinazoline **15** in excellent yield of 92% (Scheme 4). Furthermore, following optimization, we were able



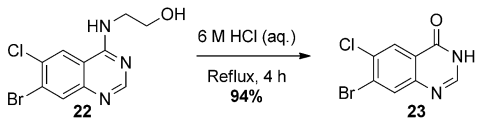
Scheme 4. Stepwise cyclization towards quinazolines.

to telescope this sequence leading to a general method for quinazoline synthesis, which is summarized in Table 2.

All substrates underwent efficient cyclocondensation under the optimized reaction conditions. A range of substitution patterns were well tolerated with the *ortho*-, *meta*- and *para*-Me substrates generating the corresponding quinazolines **16**–**18** in excellent yield. The electronic nature of the substrate was found to have a profound effect on the cyclization rate; methoxyaryl **6** provided **19** in high yield after 1 h, whereas trifluoromethyl- and halide-containing substrates required a longer time of 14 h. Nonetheless, the cyclised products were obtained in high yields in all cases.[15]

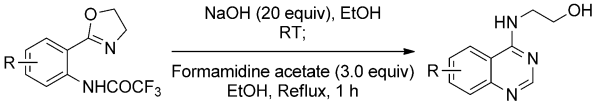
Having established the multicomponent coupling strategy, we wanted to explore their further functionalization to demonstrate their broad utility in organic synthesis. Indeed, with a view to developing a generic synthetic method to highly functionalised quinazolinones, we explored the hydrolysis of **22**. Pleasingly, subjecting **22** to aqueous acid upon heating at reflux generated the halofuginone quinazolinone **23** in an excellent yield of 94% (Scheme 5).

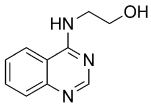
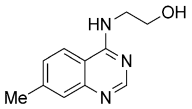
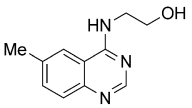
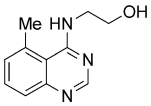
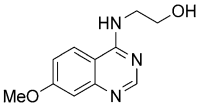
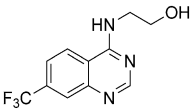
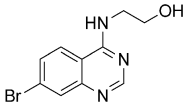
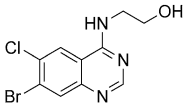
Finally, we have found our methodology to be applicable to a short and efficient synthesis of erlotinib, a tyrosine kinase inhibitor that offers treatment for several cancers including pancreatic and non-small cell lung cancer (Scheme 6).[16] Benzoic acid **24** was converted into the corresponding oxazoline **25**



Scheme 5. Synthesis of the halofuginone quinazolinone.

Table 2. Scope of the cyclization with formamidine acetate.

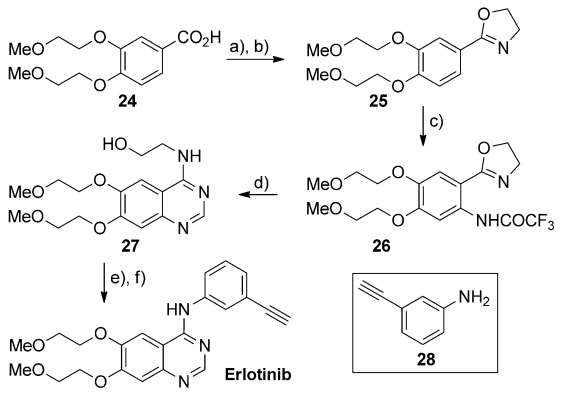


Entry	Product	Yield [%][a]
1		**15**; 89
2		**16**; 93
3		**17**; 93
4		**18**; 46[c]
5		**19**; 80
6		**20**; 93[d]
7		**21**; 79[d]
8		**22**; 83[d]

[a] Reaction conditions: trifluoroacetamide substrate (0.4 mmol), NaOH (8.0 mmol), ethanol (4.0 mL), RT, then formamidine acetate (1.2 mmol), ethanol (4.0 mL), reflux. [b] Isolated yield. [c] Hydrolysis was conducted upon heating at reflux for 2 h, followed by cyclization for 1 h. [d] Cyclization with formamidine acetate conducted over 14 h.

using a tosylation/cyclization approach in good a yield of 62%. Most gratifyingly, the C–H amidation and cyclization steps proceeded in excellent yields of 86 and 82%, respectively, to afford the highly functionalized quinazoline **27**. Hydrolysis with aqueous acid gave rise to the corresponding quinazolinone in 71% yield, which upon treatment with $POCl_3$ followed by substitution with 3-ethynlaniline **28** led to the desired compound erlotinib in 69%.

In conclusion, we reported a new and efficient multi-component synthesis of the quinazoline heterocycle from commercially available benzoic acid starting materials. Our route benefits from not only a mild and highly functional group tolerant C–H amidation step, but also a rapid cyclization step to achieve the target molecules. Furthermore, we have exemplified the utility of our approach in organic synthesis by the preparation of biologically important quinazoline motifs.



Scheme 6. Synthetic route to erlotinib. a) $(COCl)_2$, cat. DMF, CH_2Cl_2; $HO(CH_2)_2NH_2$, Et_3N (79%); b) TsCl, Et_3N, cat. DMAP, CH_2Cl_2; NaOH, MeOH (62%); c) H_2NCOCF_3, 2.5 mol% $[Cp^*RhCl_2]_2$, 10 mol%, $AgSbF_6$, $PhI(OAc)_2$, CH_2Cl_2, 40 °C, 16 h (86%); d) NaOH, EtOH; $H_2NCHNH.HOAc$, EtOH, reflux (82%); e) 6 M HCl, reflux (71%); f) $POCl_3$, PhMe, reflux; *i*PrOH, pyridine, **28**, reflux (69%).

Experimental Section

Typical C–H amidation procedure as exemplified by the formation of 2

To a flame-dried Schlenk tube was added $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol), $PhI(OAc)_2$ (97 mg, 0.30 mmol) and trifluoroacetamide (23 mg, 0.20 mmol). The tube was fitted with a rubber septum, and placed under an atmosphere of nitrogen. 2-Phenyl-2-oxazoline (59 mg, 0.40 mmol) was then added, followed by dry dichloromethane (2.0 mL). The septum was replaced by a Teflon screw cap under nitrogen flow. The reaction mixture was stirred at 40 °C for 16 h. After cooling to RT, the solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel eluting with dichloromethane to afford the aminated product as a colourless solid (48 mg, 92%). M.p. 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 13.69$ (1H, s, N*H*), 8.68 (1H, dd, $J = 8.5$ and 1.0 Hz, CH_{ar}), 7.90 (1H, dd, $J = 8.5$ and 1.0 Hz, CH_{ar}), 7.52 (1H, t, $J = 8.5$ Hz, CH_{ar}), 7.21 (1H, t, $J = 8.5$ Hz, CH_{ar}), 4.43 (2H, t, $J = 9.5$ Hz, CH_2), 4.16 ppm (2H, t, $J = 9.5$ Hz, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 164.7$, 155.7 (q, $J = 37.5$ Hz), 137.7, 132.9, 129.4, 124.5, 120.3, 116.1 (q, $J = 288.5$ Hz), 114.5, 66.8, 54.5 ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$): $\delta = -76.0$ ppm; FTIR: $\tilde{\nu}_{max}$ (neat) = 3054 (w), 2915 (w), 1734 (s), 1260 cm^{-1} (s); HRMS: *m/z* calcd for $C_{11}H_{10}N_2O_2F_3$: 259.0694 $[MH]^+$; found 259.0704.

Typical cyclization procedure as exemplified by the formation of 15

Substrate **2** (103 mg, 0.400 mmol) was dissolved in ethanol (4.0 mL), NaOH pellets (320 mg, 8.00 mmol) were added and the reaction mixture was stirred at RT. The reaction was monitored by TLC analysis until complete conversion of the starting material was observed; upon completion, the solvent was removed in vacuo. The residue was dissolved in water and ethyl acetate, and transferred to a separating funnel. The layers were partitioned, followed by further extraction of the aqueous layer with ethyl acetate. The combined organics were then washed with brine, followed by drying over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo. The residue was then dissolved in ethanol (4.0 mL) and formamidine acetate (125 mg, 1.20 mmol) was added and the mixture was heated at reflux for 1 h. After cooling to RT, the reaction mixture was dry loaded onto silica gel and purified by flash-column chromatography eluting with 10% methanol in dichloromethane to afford the quinazoline product (67 mg, 89%). M.p. 157–158 °C; ^{1}H NMR (400 MHz, $[D_6]$DMSO): $\delta = 8.44$ (1H, s, N=C*H*), 8.27 (1H, s, N*H*), 8.24 (1H, dd, $J = 8.5$, 1.0 Hz, CH_{ar}), 7.75 (1H, ddd, $J = 8.5$, 7.0, 1.0 Hz, CH_{ar}), 7.67 (1H, dd, $J = 8.5$, 1.0 Hz, CH_{ar}), 7.50 (1H, ddd, $J = 8.5$, 7.0, 1.0 Hz, CH_{ar}), 4.81 (1H, t, $J = 5.5$ Hz, O*H*), 3.67–3.57 ppm (4H, m, $(CH_2)_2$); ^{13}C NMR (100.6 MHz, $[D_6]$DMSO): $\delta = 159.5$, 155.0, 149.1, 132.5, 127.5, 125.5, 122.7, 115.0, 59.2, 43.3 ppm; FTIR: $\tilde{\nu}_{max}$ (neat) = 3233 (m), 3021 (w), 2961 (w), 1584 (s), 1319 (s), 1064 (s), 771 cm^{-1} (s); HRMS: *m/z* $[MH]^+$ calcd for $C_{10}H_{12}N_3O$: 190.0980; found: 190.0973.

Acknowledgements

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Keywords: amidation · cyclization · homogeneous catalysis · oxazolines · quinazolines

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