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Facile synthesis of 7-amino anilinoquinazolines via direct amination of the quinazoline core

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Abstract—The facile preparation of 4-(3-chloro-4-fluoroanilino)-6-alkoxy-7-aminoquinazolines from their corresponding 7-triflate and 7-fluoro precursors are highlighted.

Traditional anticancer treatments have targeted the inhibition of DNA synthesis and function. Alternative approaches selectively targeting inhibition of signalling pathways that mediate proliferation are currently the subject of much research. Epidermal growth factor receptor (EGFR) is important for growth signalling and is over-expressed in a significant number of human tumours.[1] 4-Anilinoquinazolines such as *gefitinib* (IRESSA)[2] and *erlotinib* (TARCEVA),[3] represent a potent and selective class of EGFR inhibitors which act via competitive binding at the ATP binding site of EGFR tyrosine kinase.[1] Both compounds have recently been approved for the treatment of non-small cell lung cancer refractory to chemotherapy.[4]

In our recent efforts to explore variation at positions 6 and 7 of the ring nucleus to further investigate the structure–activity, it was shown that 4-(3-chloro-4-fluoroanilino)-6-alkoxy-7-aminoquinazolines were inhibitors of the tyrosine kinase activity of EGFR. Herein, we communicate the facile and parallel chemistry employed to achieve this important class of kinase inhibitors from their corresponding 7-triflates (Scheme 1).

The synthesis of **3** started from 6-methoxy-7-benzyloxyoxyquinazolone **1**.[5] Deprotection of the benzyl ether at C-7 was achieved using TFA in the presence of water to trap the benzyl cation and prevent ring alkylation. The resulting 7-phenol was subsequently acetylated and chlorinated to afford the 4-chloroquinazoline intermediate **2**. Substitution of **2** with 3-chloro-4-fluoroaniline was achieved in excellent yield in *i*-PrOH at reflux. The phenol was revealed by treatment with ammonia in methanol and conversion of the resulting 7-hydroxy to triflate **3** was realised in 88% yield using an adapted method reported by Hendrickson and Bergeron.[6,7] Triflate **5** was prepared from *gefitinib* (**4**) with an overall yield of 62%.[8] Deprotection of the methylether at 7 was achieved in excellent yield using pyridinium hydrochloride under melt conditions. The resulting 7-hydroxy was transformed to its corresponding triflate using the same conditions as for **3** to afford **5** in acceptable overall yield.

Our initial efforts concentrated on Pd-catalysed aminations.[9] All attempts to employ Buchwald–Hartwig type chemistry to aminate either **3** or **5** failed. Attack at sulfur resulted in formation of the 7-hydroxy and after prolonged heating the reaction profile did not change. We postulate the presence of a base, which leads to formation of the anilide anion, deactivating the ring and discouraging initial oxidative addition. We next turned our attention to direct aminations of activated aryltriflates that had been previously reported on simple systems using high-pressure techniques.[10] We report a convenient process for the direct amination of the aforementioned triflates by direct aromatic nucleophilic substitution despite the deactivating positive mesomeric effect of the adjacent 6-MeO group. Previous syntheses of 7-aminoquinazolines have relied upon an activating NO_2 group at C-6.[11] A selection of secondary amines used for this reaction is listed in Table 1.[12]

Keywords: Direct amination; Triflate.
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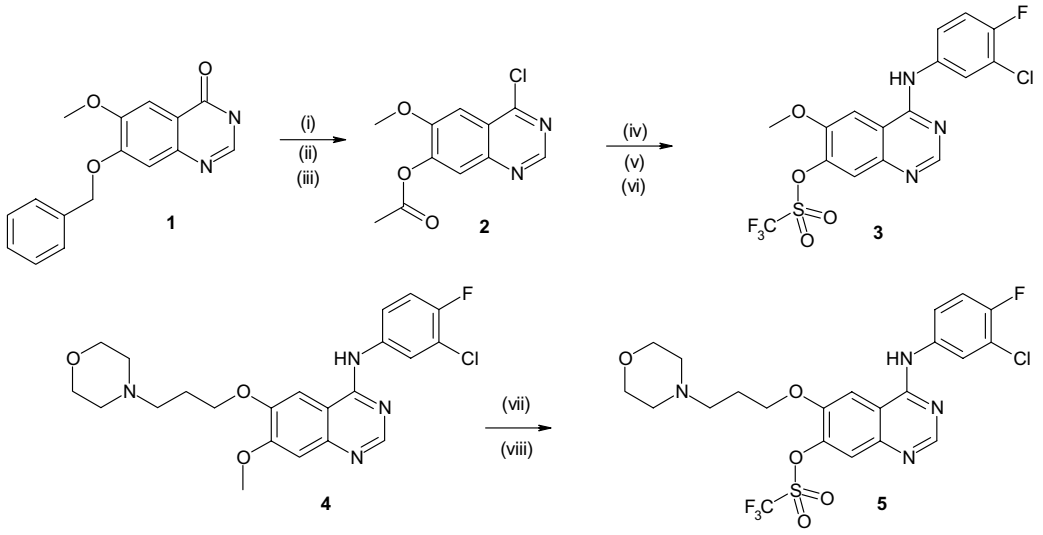
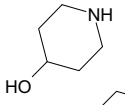
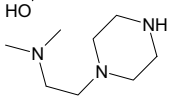
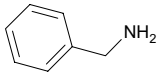
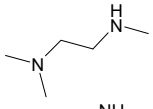
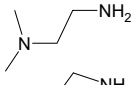
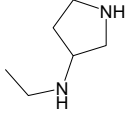
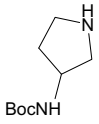
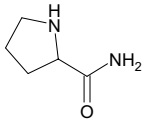


Scheme 1. Synthesis of the 7-triflates **3** and **5**. Reagents and conditions: (i) TFA–H_2O (3.75:1), reflux, 2 h, 100%; (ii) Ac_2O, pyridine, reflux, 1 h, 89%; (iii) $SOCl_2$, reflux, 1.5 h, 69%; (iv) 3-chloro-4-fluoroaniline, *i*-PrOH, reflux, 91%; (v) NH_3/MeOH, rt, 2 h, 90%; (vi) $PhN(Tf)_2$, K_2CO_3, THF, rt, 88%; (vii) pyridinium hydrochloride, 170 °C, 3 h, 80%; (viii) $PhN(Tf)_2$, K_2CO_3, THF, rt, 77%.

Table 1. Isolated yields quoted after purification by silica gel column chromatography[12]

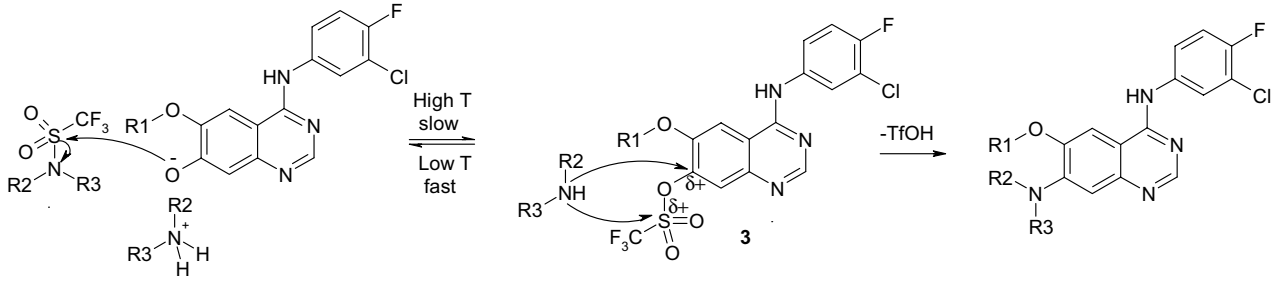
Entry	Amine	Yield (%) (from **3**)	Yield (%) (from **5**)
1		64	55
2		72	78
3		35	53
4		67	45
5		20	10
6		77	44
7[a]		20	14
8		54	78
9		95	85
10		58	65

[a] Compounds not isolated.

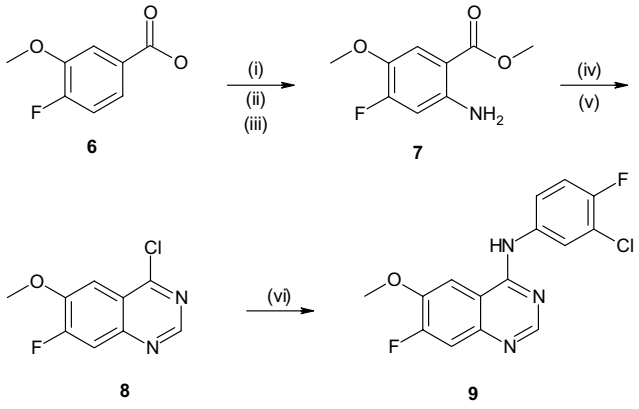
Best results were achieved by adding the solid triflate to 5 equiv of amine at 135 °C in *N*-methylpyrrolidinone over a period of 5–10 min and stirring the resulting solutions for 2–5 h. The main impurity was the 7-phenol, which was easily removed by chromatography. As expected, the more nucleophilic amines gave the cleanest conversions. Alcohol functionality was tolerated (entry 3). Primary amines gave consistently poor yields (e.g., entry 7). Reaction of amines having two available sites (entry 8) resulted in attack entirely from the least hindered and most nucleophilic site (*endo*) as determined by NOESY NMR. The conditions also supported the base stable protecting groups (e.g., entry 9) and amide functionality (entry 10).

We hypothesise that the mechanism actually passes by two stages (Scheme 2). Exposure of the triflates to an excess of amine at room temperature may result in an equilibrium in which attack at sulfur affords the tertiary triflamide and the kinetic product, the 7-phenoxide. Upon heating the mixture, the triflate is eventually trapped out of the equilibrium as the desired thermodynamic 7-aminoquinazoline product in respectable to excellent yields. The mechanism is supported by LCMS. It was observed that displacement of the 7-triflates with primary amines gave in general poor yields of the desired product. This maybe due to a combination of the greater stability of the secondary triflamide formed in the first part of the equilibrium[13] and the reduced nucleophilicity of primary over secondary amines.

As mentioned above, attempted aminations of **3** or **5** with primary amines did not afford high yields. Therefore, to enable the preparation of a small library of secondary amine analogues, a 7-fluoro quinazoline was prepared where it was speculated, as in the case of the 7-OTf, the activation of position 7 by the quinazoline ring should overcome any deactivating positive



Scheme 2. Proposed mechanism of direct amination of **3** supported by LCMS.



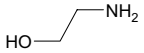
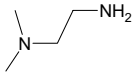
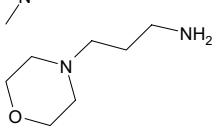
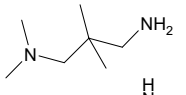
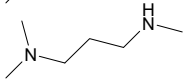
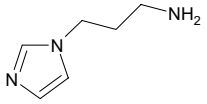
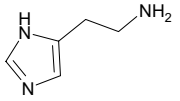
Scheme 3. Synthesis of 4-(3-chloro-4-fluoroanilino)-6-methoxy-7-fluoroquinazoline (**9**). Reagents and conditions: (i) MeOH, cat. H_2SO_4, reflux, 16 h, 95%; (ii) HNO_3, H_2SO_4, 0–10 °C, 0.5 h, 62%; (iii) H_2, Pd–C, EtOH, rt, 6 h, 89%; (iv) formamide, acetic acid, 135 °C, 68%; (v) $SOCl_2$, reflux, 16 h, 95%; (vi) 3-chloro-4-fluoroaniline, *i*-PrOH, reflux, 91%.

mesomeric influence by the adjacent 6-MeO group (Scheme 3).

The preparation of **9** was achieved in a straightforward manner from the commercially-available benzoic acid **6**. Esterification followed by regiospecific nitration and reduction afforded a good overall yield of anthranilic acid derivative **7**, which was cyclised in the presence of formamide and chlorinated using standard conditions to afford 4-chloroquinazoline **8**. Substitution of **8** with 3-chloro-4-fluoroaniline allowed us to access large quantities of **9** in excellent yield, which was used without further purification.

Amination of **9** was achieved using a 5-fold excess of amine in *N*-methylpyrrolidinone at 135 °C in the presence of potassium carbonate. We found that non-nucleophilic tertiary amine bases, for example, DIPEA were not useful in this reaction. The mole of HF generated was not irreversibly neutralised and this led to degradation of the side chain post-substitution at 135 °C as indicated by LCMS. We postulate that potassium carbonate plays two roles in the reaction: (1) irreversibly neutralising the mole of HF generated by the substitution; (2) and offering a significant energy sink through the enthalpy of formation of KF (Table 2).

Table 2. Isolated yields quoted after purification by silica gel chromatography[14]

Entry	Amine	Yield (%)
1		83
2		76
3		92
4		67
5		57
6		77
7		66
8		58
9		65
10		89

As for the 7-triflate, the cleanest conversions were observed with the most nucleophilic amines. The reaction conditions tolerated alcohol functionality (entry 3) and heteroaromatic bases, such as imidazole (entry 10), also reacted in excellent yield.

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5. Starting from commercially-available vanillic acid, a similar process was used to access **3** as described by Pandey, A.; Volkots, D.; Sergooy, J. M.; Rose, J. W.; Yu, J.-C.; Lambing, J. L.; Hutchaleelaha, A.; Hollenbach, S. J.; Abe, K.; Giese, N. A.; Scarborough, R. M. *J. Med. Chem.* **2002**, *45*, 3772.
6. Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *14*, 4607.
7. Classical conditions (Tf_2O, pyridine, DCM) proved unreliable to form the 7-OTf. During the reaction, equilibrium is quickly established where the 7-OTf, once formed, is attacked at sulfur by pyridine to afford the 7-phenol. To prevent an equilibrium forming, phenyl-*N*(bis) trifluoromethanesulfonamide was used with considerable success. Typically: to a stirred slurry of the phenol (1.00 equiv) and K_2CO_3 (Aldrich −325 mesh, 3.00 equiv) in THF (5 ml/g), was added solid phenyl-*N*(bis) trifluoromethanesulfonamide (1.01 equiv). The slurry was stirred at ambient temperature for 4 h. The slurry was filtered through a bed of Celite and concentrated on a rotary evaporator to afford a thick viscous oil which was recrystallised from ice-cold methanol (3 ml/g) to afford the triflate (88%) as an off-white solid.
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11. (a) Ding, S.; Gray, N. S.; Wu, X.; Ding, O.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594; (b) Tobe, M.; Isobe, Y.; Tomizawa, H.; Matsumoto, M.; Obara, F.; Nagasaki, T.; Hayashi, H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 545.
12. Typically: the amine (5.00 equiv) in NMP (1 ml/g) is heated to 135 °C. The 7-OTf (1.00 equiv) is added and the reaction temperature maintained for a further 3–5 h. The reaction mixture is loaded onto pre-packed silica gel cartridges and purified eluting with DCM to NH_3–MeOH–DCM gradient.
13. When the triflate is added at 135 °C, attack at sulfur in the first part of the equilibrium is to a degree by-passed and the desired products can be isolated, in certain cases, in yields as high as 20%.
14. Typically: the 7-fluoroquinazoline (1.00 equiv), K_2CO_3 (1.10 equiv) and amine (5.00 equiv) in NMP (1 ml/g) are heated to 135 °C for 5 h. The reaction mixture is loaded onto pre-packed silica gel cartridges and purified eluting with DCM–NH_3–MeOH–DCM gradient.