A New Synthesis of Gefitinib

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Abstract A four-step synthesis of the FDA-approved anticancer agent gefitinib was developed starting from 2,4-dichloro-6,7-dimethoxyquinazoline. Reaction temperatures were highly practical (0–55 °C), and chromatographic purifications were avoided. The ionic liquid trimethylammonium heptachlorodialuminate was used to monodemethylate the dimethoxyquinazoline core. In the final step, a selective dehalogenation was employed to provide gefitinib in 14% overall yield on a gram scale.

Key words ionic liquids, demethylation, nucleophilic aromatic substitution, dehalogenation, gefitinib, medicinal chemistry

Originally developed by AstraZeneca, gefitinib (Iressa) is a small-molecule tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR).1 The drug was approved in 2015 by the US Food and Drug Administration (FDA) as a first-line treatment for metastatic non-small-cell lung cancer (NSCLC) with EGFR mutations. Worldwide, lung cancer is the most prevalent fatal cancer for both men and women.2 In NSCLC, mutation of the EGFR tyrosine kinase domain destabilizes the kinase conformation and affects downstream signaling pathways.3 These disruptions stimulate cancer cell proliferation and inhibit apoptosis. Gefitinib reversibly binds to the ATP site of the EGFR kinase domain to inhibit autophosphorylation and signal transduction.4 Several syntheses of gefitinib have been described in the literature.5–9 AstraZeneca’s original synthesis began with the demethylation of 6,7-dimethoxyquinazoline-4-one with L-methionine and methanesulfonic acid, followed by acetylation, halogenation, aniline nucleophilic aromatic substitution (SNAr), deacetylation, and O-alkylation (Scheme 1).10 This six-step synthesis (10% overall yield) required chromatographic purifications and used hazardous reagents, such as thionyl chloride, which reacts violently with water to produce toxic fumes of sulfur dioxide and also contaminates the air very quickly upon evaporation at 20 °C.11

In 2007, Reddy and co-workers reported a synthesis of gefitinib from isovanillin (Scheme 2).12 The nitro group in the isovanillin-derived intermediate was reduced with sodium dithionite, followed by treatment with N,N-dimethylformamide dimethylacetal (DMF-DMA; 1,1-dimethoxy-
N,N-dimethylmethanamine) and amination with 3-chloro-4-fluoroaniline to yield the active pharmaceutical ingredient (API). No chromatography was required, but high reaction temperatures were needed, and DMF was used in large quantities in the seven-step synthesis.

More recently, Suh and co-workers reported a variant of the AstraZeneca synthesis that used a transient-protective-group strategy (Scheme 3). An acetylated quinazoline core was subjected to a chlorination with POCl₃, substitution with 3-chloro-4-fluoroaniline, and deprotection with LiOH to set the stage for alkylation with 4-(3-chloropropyl)morpholine, using TMSI to protect the aniline nitrogen transiently. Although high yielding, this synthetic route required hazardous TMSI and a more-elaborate starting material. It also used phosphoryl chloride, which reacts violently with water to produce toxic gases, and is highly corrosive.

We envisioned a new route to gefitinib with fewer than five steps from inexpensive starting materials that would avoid hazardous reagents and chromatographic separations, and would keep reaction temperatures in the 0–60 °C range. Such a process would be commercially relevant and potentially attractive for pharmaceutical manufacturing. To increase the electrophilic reactivity of the pyrimidine moiety in the SₕAr reaction, we chose commercially available 2,4-dichloro-6,7-dimethoxyquinazoline (1) as a starting material. To the best of our knowledge, a synthesis of gefitinib or related analogues that utilizes a 2,4-dichloro-quinazoline as a starting material or advanced intermediate is unprecedented. We reasoned that the SₕAr substitution of the chlorine in the 4-position of the quinazoline would occur preferentially, and that the 2-position might be readily dechlorinated at a late stage. We did not employ a Buchwald–Hartwig amination of the quinazoline because of concerns regarding the harsh conditions often required and because of the risk of contaminating the API with Pd. Furthermore, several groups have recently demonstrated the feasibility of nucleophilic aromatic substitutions on similar quinazoline substrates under simple acidic conditions.

Accordingly, the dichloroquinazoline 1 was treated with 3-chloro-4-fluoroaniline in 20.4 equivalents of acetic acid at 55 °C for two hours to yield the coupling product 2 after extraction with EtOAc and filtration (Scheme 4). Under these conditions, we were able to isolate the desired 4-aminated product 2 exclusively in 65% yield on a multigram scale. Not unexpectedly, however, the ensuing selective demethylation of 2 proved challenging (Table 1). A variety of conditions were tested, including L-methionine in methanesulfonic acid. However, these conditions mainly afforded decomposition products at the high temperatures that proved necessary for significant conversion. Interestingly, BB₃ provided the bisdemethylated product exclusively (entry 2). When we experimented with...
various additives to BBr$_3$ to control the rate of demethylation, we either observed no reaction (NR) or a complex mixture of products (entries 3 and 4). Another Lewis acid, aluminum iodide (AlI$_3$), also showed no reaction at low temperatures (entry 5). Aluminum chloride (AlCl$_3$) showed a robust rate of conversion but, even in the presence of sodium iodide (NaI), at best provided a 1:1 ratio of demethylated isomers that were difficult to separate (entries 6–7). With ethanethiol as an additive, a favorable 1:0.4 ratio was obtained, but in low yield (entry 8). Reaction times longer than two days were required for high conversions.

In an attempt to accelerate the reaction without recourse to excessive heating that could potentially lead to deamination byproducts and quinazoline ring opening, we explored the cleavage of methyl ethers through the use of ionic liquid (IL) reagents, including trimethylammonium heptachlorodialuminate ($\text{TMAH}[\text{Al}_2\text{Cl}_7]$). The IL demethylation mechanism is similar to that of AlCl$_3$; however, the IL contains a higher concentration of chloride ions, the nucleophilicity of which is enhanced, resulting in shorter reaction times. Furthermore, improved demethylation selectivity has been reported for bicyclic ring systems. The IL was synthesized in situ from aluminum trichloride and trimethylammonium chloride in dichloromethane, and was direct-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent(s) (equiv)</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Product(s)$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>l-methionine (1.2)</td>
<td>150</td>
<td>MsOH</td>
<td>– (dec.)</td>
</tr>
<tr>
<td>2</td>
<td>BBr$_3$ (3.0)</td>
<td>r.t.</td>
<td>CH$_2$Cl$_2$</td>
<td>7$^b$</td>
</tr>
<tr>
<td>3</td>
<td>ZrCl$_2$ (2.0), BBr$_3$ (1.0)</td>
<td>50</td>
<td>CH$_2$Cl$_2$</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>TiCl$_4$ (2.0), BBr$_3$ (1.0)</td>
<td>45</td>
<td>CH$_2$Cl$_2$</td>
<td>mixture</td>
</tr>
<tr>
<td>5</td>
<td>AlI$_3$ (1.5), PhSH (1.5)</td>
<td>0</td>
<td>CH$_2$Cl$_2$</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>AlCl$_3$ (3.0)</td>
<td>r.t.</td>
<td>CH$_2$Cl$_2$</td>
<td>3, 6$^c$</td>
</tr>
<tr>
<td>7</td>
<td>AlCl$_3$ (3.0), NaI (3.0)</td>
<td>r.t.</td>
<td>CH$_2$Cl$_2$</td>
<td>3, 6</td>
</tr>
<tr>
<td>8</td>
<td>AlCl$_3$ (3.0), EtSH (2.0)</td>
<td>40</td>
<td>CH$_2$Cl$_2$</td>
<td>3, 6$^d$</td>
</tr>
<tr>
<td>9</td>
<td>$\text{TMAH}[\text{Al}_2\text{Cl}_7]$ (3.0)</td>
<td>50</td>
<td>CH$_2$Cl$_2$</td>
<td>3, 6$^e$</td>
</tr>
</tbody>
</table>

$^*$ Products and product ratios were determined by LC/MS and $^{19}$F NMR analyses.

$^b$ The bisdemethylated product 7 was formed exclusively.

$^c$ A 1:3 ratio of demethylated isomers and the starting material was detected that could not readily be enriched in the desired product through crystallization.

$^d$ A 1:0.4 ratio of phenols 3 and 6 was formed in low yield.

$^e$ A 1.3:1 ratio of phenols 3 and 6 was enriched to a 97:3 ratio in the first crystallization batch favoring the desired product 3.
ly used for the demethylation step in a one-pot protocol. With intermediate 2, we found that treatment with [TMAH][Al2Cl7] at 50 °C for two hours gave a 1.1–1.3 to 1 ratio of monodemethylated regioisomers; however, a favorable >95:5 ratio of the desired product could be obtained in 30–35% yield without chromatography by crystallization of the concentrated reaction mixture from hot methanol. Although not required for the next step, a second crystallization increased the regioisomeric purity to >99%.

The IL was freshly prepared before each use, and was not concentrated as suggested in the original publication,19 because we found that removal of the solvent generally resulted in a less active reagent. The one-pot protocol also simplified the experimental protocol. Significantly, the synthesis of [TMAH][Al2Cl7] IL is cost effective, and its feasibility for chemical-process applications has already been demonstrated on 7 kg scale.20

Previous syntheses mainly used DMF, sodium and potassium carbonates, and high temperatures for the O-alkylation step. We found that sodium and potassium carbonates were not effective at low temperatures in DMSO. In contrast, the reaction of 3 with 4-(3-chloropropyl)morpholine in the presence of cesium carbonate in DMSO at 40 °C for 2.5 hours provided ether 4 in 80% yield after filtration and crystallization from hot methanol. The FDA classifies DMF as a more-hazardous Class 2 solvent, whereas DMSO is a less-hazardous Class 3 solvent; therefore, these conditions were in agreement with our goal of minimizing the use of toxic or controlled reagents.21

The final dehalogenation step in the conversion of 4 to 5 required considerable optimization. Palladium(II) acetate in the presence of hydrogen gas provided no control of selectivity and resulted in complete dechlorination to 8 (Figure 1), as well as loss of aniline, among other side reactions. Similarly, hydrogenation with 10% Pd on carbon resulted in the loss of the quinazoline chlorine as well as the aniline chlorine atoms to give predominantly 8. Attempts at hydrogenation by using Lindlar’s catalyst or Raney nickel both provided only trace conversions to the desired product 5, along with varying amounts of the bisdechlorinated derivative 8. Similarly unsatisfactory results were obtained by using a combination of NaBH4 and TMEDA under palladium catalysis.22 However, a chemoselective conversion was finally realized by using zinc and acetic acid in the presence of tetrabutylammonium bromide (Bu4NBr) as an additive, a reagent combination that had previously been shown to reduce a chloropyridine substrate selectively.23 In addition to the desired product 5, under these conditions we also observed that small amounts of 2-chloro-4-fluoroaniline were formed, which probably originated from an acid-mediated solvolysis of the quinazoline moiety. This side reaction could be suppressed through a modification employing zinc and N,N,N′,N′-tetramethylethylenediamine (TMEDA) in a mixture of MeOH and AcOH to achieve the desired dehalogenation of 4 exclusively. After stirring the reaction mixture at 40 °C for 24 hours, 2-mercaptanonic acid was added to assist in the removal of excess zinc and zinc salts.24 Finally, we were able to crystallize the product from hot MeOH to provide gefitinib (5) as colorless crystals in 82% yield with >99% purity as determined by LC/MS analysis.25

In conclusion, a gram-scale synthesis of gefitinib was accomplished in four steps from commercially available 2,4-dichloro-6,7-dimethoxyquinazoline. Reaction temperatures did not exceed 55 °C, and workup procedures took advantage of the superior crystallization properties of the (C2)-chlorinated quinazolines in methanol. Thus, all purifications were performed by filtrations or crystallizations. No protective groups were required, and reagents such as DMF, SOCl2, POCl3, and TMSI were avoided. A new application of an ionic liquid streamlined the demethylation step, and a selective dehalogenation by using zinc, acetic acid, and TMEDA proved successful.

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2-Chloro-N-(3-chloro-4-fluorophenyl)-6,7-dimethoxyquinazolin-6-ol (3)

A suspension of quinazolinamine 

2-Chloro-4-[(3-chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-ol (3)
hot MeOH (100 mL), heated to reflux for 10 min, and then allowed to cool and precipitate for 6 h while stirring was maintained. The solid was collected by filtration, washed with MeOH (10 mL) and dried in vacuo (0.5 Torr, 20 °C) to give a white solid consisting of a 97:3 mixture of regioisomers; yield: 1.26 g (3.56 mmol, 6%).

**Major Regioisomer 3**

Mp 335.4–336.7 °C; TLC: Rf = 0.4 (5% MeOH–CH2Cl2); IR (ATR, neat): 3329, 2813, 1945, 1623, 1578, 1499, 1430, 1290, 1211, 1149, 1110, 1013, 960, 852, 735 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ = 10.67 (s, 1 H). ¹³F NMR (376 MHz, DMSO-d₆): δ = –122.0; HRMS (LC/MS, ESI⁺): m/z [M + H]+ calcd for C₁₅H₁₁Cl₂FN₄O₁₂: 481.1204; found: 481.1203.

**Characteristic Signals for Minor Regioisomer:** 2-Chloro-4-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholino-propoxy)quinazolin-4-amine (4)

A solution of quinazolinol (3) (1.25 g, 3.53 mmol), 4-(3-chloro-propyl)morpholine (0.59 mL, 3.9 mmol), and Cs₂CO₃ (2.30 g, 0.090 g; mp 188.5–190.6 °C), containing residual MeOH (~4%), was further dried in vacuo (0.5 Torr, 80 °C) for 24 h to provide a colorless solid (yield: 1.06 g, 2.41 mmol) which was collected by filtration and dried in vacuo (0.5 Torr, 20 °C) to provide a colorless solid; yield: 0.93 g (2.08 mmol, 82%); mp 195.7–197.5 °C; TLC: Rf = 0.2 (EtOH–EtOAc–hexanes); IR (ATR, neat): 3365, 3160, 1873, 2816, 1622, 1578, 1530, 1497, 1472, 1426, 1393, 1353, 1280, 1217, 1112, 1044, 993, 957, 850, 772 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ = 9.57 (s, 1 H), 8.50 (s, 1 H); 8.11 (dd, J = 6.8, 2.8 Hz, 1 H), 7.81 (s, 1 H), 7.80–7.77 (m, 1 H), 7.45 (app t, J = 9.2 Hz, 1 H), 7.21 (s, 1 H), 4.18 (t, J = 6.0 Hz, 2 H), 3.94 (s, 3 H), 3.58 (app t, J = 4.4 Hz, 2 H), 2.39 (br s, 4 H), 2.03–1.96 (m, 2 H). ¹³C NMR (100 MHz, DMSO-d₆): δ = 156.0, 154.5, 152.6, 151.9, 148.3, 147.0, 136.8, 123.5, 122.4, 118.8, 118.7, 116.6, 116.4, 108.8, 107.3, 102.5, 67.1, 66.2, 55.9, 55.0, 53.4, 25.9. ¹⁹F NMR (376 MHz, DMSO-d₆): δ = –123.3; HRMS (LC/MS, ESI⁺): m/z [M + H]+ calcd for C₂₂H₂₃ClF₅N₆O₃: 476.1594; found: 474.1593.