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Practical and efficient synthesis of gefitinib *via* selective *O*-alkylation: A novel concept for a transient protection group

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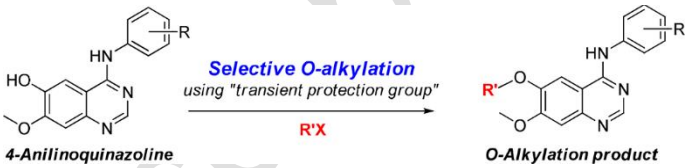
Supporting Information: Full experimental detail, ^{1}H and ^{13}C NMR spectra, HPLC traces, HRMS spectra, and EA data. This material can be found *via* the "Supplementary Content" section of this article's webpage.

ABSTRACT

A practical process that includes a simple four-step procedure for the preparation of gefitinib (**1**), a tyrosine kinase inhibitor that targets the epidermal growth factor receptor, is described. Dramatic improvements over previously reported conventional synthetic procedures were achieved. We found effective coupling conditions to minimize the inevitable production of an *N*-alkylated side product, *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)-*N*-(3-morpholinopropyl)-quinazoline-4-amine (**3**) by using a transient trimethylsilyl protecting group. We synthesized gefitinib in an 81.1% overall yield from a commercially available starting material on a multigram scale using a route that did not require work-up of any of the reaction steps.

GRAPHICAL ABSTRACT



KEYWORDS: anilinoquinazoline, EGFR inhibitor, gefitinib, transient protection group

Introduction

Quinazoline derivatives, especially 4-anilinoquinazolines, have been prevalent motifs in pharmaceutical molecules in recent years, notably as an Epidermal Growth Factor Receptor

(EGFR) inhibitor.[1] As shown in **Figure 1**, several representative current drugs contain 4-anilinoquinazoline as a core part.

It was revealed that the quinazoline moiety interacts with the hinge domain of the kinase and the aniline moiety inserts into the hydrophobic pocket; these are crucial interactions for EGFR inhibitory activity. The side chains at the C-6 and C-7 positions are not a part of the pharmacophore, which makes long ether chains or other corresponding moieties compatibile.[2–5] Therefore, many novel EGFR inhibitors have been designed and synthesized by incorporating an alkoxy moiety *via* *O*-alkylation of the hydroxyl group at the C-6 or C-7 position of the 4-anilinoquinazoline scaffold.[6–13] However, in most alkylations of anilinoquinazolines that used an alkyl halide, a mixture of *O*- or *N*-alkylated as well as *N*,*O*-dialkylated products were produced without satisfactory selectivity. In addition, purification of the alkylation product is known to be tedious. Thus, the development of new synthetic strategies that provide selective *O*-alkylation of the 4-anilinoquinazoline moiety is of interest for both laboratory and industrial preparation of EGFR inhibitors.

Gefitinib,[14] the first selective inhibitor of the EGFR kinase domain, was approved in May 2003 for the treatment of recurrent NSCLC (non-small cell lung cancer).[15] Since then, gefitinib has been widely used, and synthetic methods for its preparation based on the 4-anilinoquinazoline moiety have been continuously reported.[16–22] According to a previous report,[19] gefitinib was synthesized from 6,7-dimethoxy quinazolin-4-one starting material *via* sequential selective demethylation, condensation with chlorofluoroaniline, and introduction of a 3-morpholinopropoxy side chain at the C-6 position of 4-anilinoquinazoline. This procedure afforded an excess of an *N*-alkylated side product **3**in the final step. This *N*-alkylated impurity was removed by column chromatography, which lowered the yield of gefitinib and limited the utility of this procedure for

commercial production. To overcome this problem, an improved process for the synthesis of gefitinib using 3-hydroxy-4-methoxy benzonitrile has been reported.[20] The procedure included the introduction of a morpholinopropyl group prior to the formation of the quinazoline ring in order to suppress *N*-alkylation, which required extra steps that made this process inefficient and uneconomical.

Currently, *O*-alkylation products that contain an amino group are prepared by nitro reduction or *via* sequential amine protection, alkylation of the hydroxyl group and amine deprotection. The amino group is generally protected with an acetyl or phthalyl group, which requires harsh removing conditions. Thus, expensive *tert*-butoxycarbonyl (Boc) or benzoxycarbonyl (Cbz) protecting groups are also utilized.

Recently, we have developed a selective *O*-alkylation procedure using a transient trimethylsilyl (TMS) protecting group.[21] The TMS group was attractive to us due to its high *N*-alkylation suppressing ability and its facile removal through a simple work-up. As predicted, this new and unique process minimized the generation of the *N*-alkylated side product. We also confirmed that our process is well applicable to a variety of 4-anilinoquinazolines. Herein, we describe our recent studies on the selective *O*-alkylation of 4-anilinoquinazolines as illustrated in **Figure 2** and the application of the method to a highly practical and efficient synthesis of gefitinib.

Results and Discussion

We initially investigated the selective *O*-alkylation of intermediate **2** to prevent undesired *N*-alkylation. We explored the effect of the amine salt, catalyst, and protecting group (**Table 1**) in order to develop a sustainable and economical process. Use of the acid-amine salt as a masking group for aniline resulted in a 13.5% yield (entry 1) of the *N*-alkylation product after completion

of the reaction. The use of DMAP or KI as a catalyst gave poor results (entries 2 and 3, respectively). Interestingly, transient protection with TMSI in the presence of DMAP as a catalyst afforded only 0.3% of the *N*-alkylation product (entry 5), compared to approximately 30% for the previously known method.[19] In addition, the *N*-alkylated impurity was completely removed by a simple purification process. The postulated mechanism for the selective *O*-alkylation is depicted in **Figure 3**.

Upon reaction of hydroxyquinazoline (**2**) with an alkylating agent in the presence of base, catalyst, and either HCl or TMSI, initial TMS binding to the aniline amine affords the tertiary amine intermediate (**4**), which is essentially a TMS-protected form of substrate **2**. Due to the steric hindrance of tertiary amine **4**, the amino group seems no longer reactive for alkylation and the less hindered phenolic hydroxyl group is reactive. Therefore, the *O*-alkylated intermediate **5** is formed through selective *O*-alkylation with morpholinopropyl chloride. The TMS group was easily removed with water during a simple work-up procedure to obtain gefitinib in high purity. The transient TMS-protection of the amino group prevented the *N*-alkylation reaction. We confirmed the postulated mechanism by analyzing the NMR spectra of the proposed intermediates.

Next, we explored the applicability of the selective *O*-alkylation reaction to other anilinoquinazoline moieties. As in the case of gefitinib, selective *O*-alkylation using transient protection was possible for a variety of anilinoquinazolines regardless of the aniline substituents and the alkylation reagent (**Table 2**).

We further examined the selective *O*-alkylation of synthetically important aminophenol moieties under the optimized conditions, as shown in **Table 3**. Primary amines preferentially afforded the *di*-alkylation product resulting from both *O*- and *N*-alkylation (**10**, **11**). As anticipated, 3-(phenylamino)phenol showed good selectivity for the *O*-alkylation product **12**. However,

alkylation of 3-(benzylamino)phenol produced only the *N*-alkylated product **13**, which is likely due to the steric hindrance of amino alcohols and the good nucleophilicity of arylalkyl amine.

Deacetylation of **14** according to a reported procedure[19] (r.t., 17 h and then reflux, 1.5 hr) produced 4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-ol (**2**) along with unreacted **14** (approximately 2%), which ultimately affected the purity of the final gefitinib product. Thus, an additional purification process to remove the remaining **14** was necessary, which limited the utilization of the procedure in commercial production. We have also examined other reported deacetylation conditions[23] as shown in **Table 4**. Deacetylation of **14** (entry 4) by a lithium hydroxide treatment was completed in 0.5 h and less than 0.1% of unreacted **14** was observed. Deacetylation of **14** with sodium hydroxide (entry 2) or potassium hydroxide (entry 3) was completed in 1 hr, which is shorter than that with NH_4OH (18.5 hr), with only approximately 0.1% of **14** remaining. However, an additional procedure to remove the Na or K adduct was still necessary because the byproducts were less soluble in the MeOH and water solution used for deacetylation. Fortunately, the Li adduct was more soluble in the MeOH and water solution, and the byproduct was easily removed by filtration of the reaction mixture.

Using the established procedures, we completed the synthesis of gefitinib in four reaction steps starting from 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl acetate (**15**), as illustrated in **Scheme 1**. Chlorination of quinazolone **15** followed by condensation with 3-chloro-4-fluoroaniline at 65°C afforded **14**in quantitative yield. Acetoxyquinazoline **14** was conveniently converted to hydroxyquinazoline **2** with 90% yield after lithium hydroxide treatment in a mixture of MeOH and water (1:1). Finally, facile alkylation of hydroxyquinazoline **2** with 4-(3-chloropropyl)morpholine in the presence of TMSI followed by purification by recrystallization afforded gefitinib (**1**) in greater than 99% purity by HPLC.

Experimental

^{1}H spectra and ^{13}C spectra were recorded using a Bruker DPX 400 Spectrometer. All purity values were obtained by HPLC analysis using HPLC 1200 Series from Agilent Technologies. Chemical shifts were expressed in parts per million (ppm, δ) downfield from tetramethylsilane and were referenced to the DMSO-d_6 (2.49ppm for ^{1}H and 39.5ppm for ^{13}C, respectively). ^{1}H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonances), number of protons, and coupling constant in hertz (Hz). High resolution mass spectra were obtained with a Synapt G2 instrument. Elemental analysis data were obtained on a Flash 1112 instrument (CE instrument).

HPLC analysis

Hypersil C18, 4.6 × 250 mm (5 μm), λ = 250 nm, flow rate 1.0mL /min, mobile phase (60:40) buffer/acetonitrile (buffer 5mol % ammonium acetate aqueous solution).

Selective O-alkylation of 4-anilinoquinazoline moieties with an assistance of TMSI (Table 2)

General procedure 1 (without TMSI)

To a suspension of a 6-hydroxy quinazoline compound (2.0 mmol) in dimethylsulfoxide (6.0 mL) was slowly added potassium carbonate (7.0 mmol) and 4-(3-chloropropyl)morpholine (2.4 mmol). The mixture was heated to 80°C and stirred for 2 h (termination of the reaction was confirmed by HPLC and TLC analysis). The reaction mixture was cooled to 20°C and purified water (12.0 mL) was slowly added. The mixture was stirred for 30min and the precipitate was

collected by filtration, washed with purified water (12.0 mL), and dried for 3 h at 50°C to give a 6-alkoxy quinazoline as pale yellow powder.

General procedure 2 (with TMSI)

To a suspension of a 6-hydroxy quinazoline (2.0 mmol) in dimethylsulfoxide (6.0mL) was added potassium carbonate (7.0 mmol). The mixture was cooled to −10°C and iodotrimethylsilane (2.0 mmol) was slowly added. The mixture was stirred for 1 h at 15°C and 4-(3-chloropropyl)morpholine (2.4 mmol) was slowly added. The mixture was heated to 80°C and stirred for 2 h (termination of the reaction was confirmed by HPLC and TLC analysis). The reaction mixture was cooled to 20°C and purified water (12.0mL) was slowly added. The mixture was stirred for 30min and the precipitate was collected by filtration, washed with purified water (12.0mL), and dried for 3 h at 50°C to give a 6-alkoxy quinazoline compound as pale yellow powder.

Alkylation of amino alcohols (Table 3)

General procedure

To a suspension of an amino alcohol (2.0 mmol) in dimethylsulfoxide (6.0mL) was added potassium carbonate (7.0 mmol). The mixture was cooled to -10°C and iodotrimethylsilane (2.0 mmol) was slowly added. The mixture was stirred for 1 h at 15°C and 4-(3-chloropropyl)morpholine (2.4 mmol) was slowly added. The mixture was heated to 80°C and stirred for 2 h (termination of the reaction was confirmed by HPLC and TLC analysis). The reaction mixture was cooled to 20°C and purified water (12.0mL) was slowly added. The mixture

was stirred for 30min and the precipitate was collected by filtration, washed with purified water (12.0mL), and dried at 50°C for 3 h to give an alkylated amino alcohol as pale yellow powder.

N-(3-Chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazoline-4-amine (1, Gefitinib)

To a suspension of **2** (645.0g , 2.02mol) in *N*,*N*-dimethylformamide (6.5 L) were added potassium carbonate (975.9g , 7.06mol) and *N*,*N*-dimethylaminopyridine (24.7g , 0.20mol). The mixture was cooled to -10°C and iodotrimethylsilane (404.2g , 2.02mol) was slowly added. The mixture was stirred for 1 h at 15°C and 4-(3-chloropropyl)morpholine (396.7g , 2.42mol) in *N*,*N*-dimethylformamide (645.0mL) was slowly added. The reaction mixture was heated to 80°C, stirred for 2 h (termination of the reaction was confirmed by HPLC and TLC analysis), and cooled to 20°C. After purified water (14.2 L) was slowly added, the resulting mixture was stirred for 30min and the precipitate was collected by filtration, washed with purified water (645.0mL), and dried for 3 h at 50°C to give gefitinib as pale yellow powder (812.3g , 90.1%). HPLC purity: 99.21% (the *N*-alkylating byproduct was not detected). ^{1}H-NMR (400MHz , DMSO-d_6): δ 1.95-2.02 (m, 2H), 2.38 (br, 4H), 2.45-2.50 (m, 2H), 3.56-3.58 (m, 4H), 3.93 (s, 3H), 4.17 (t, 2H, J = 6.3Hz), 7.19 (s, 1H), 7.44 (t, 1H, J = 9.1Hz), 7.76-7.80 (m, 2H), 8.10 (dd, 1H, J = 4.2Hz , 2.6Hz), 8.49 (s, 1H), 9.57 (s, 1H). ^{13}C NMR (175MHz , DMSO-d_6): δ 156.5, 155.0, 154.3, 153.1, 152.9, 148.8, 147.4, 137.3, 124.0, 122.8, 119.3, 119.2, 117.0, 109.2, 107.8, 103.0, 67.6, 66.7, 56.3, 55.4, 53.9, 26.3. HRMS: Calcd for $C_{22}H_{24}ClFN_4O_3$ [M + H] + 447.1594; Found 447.1599. Elemental Anal. Calcd for $C_{22}H_{24}ClFN_4O_3$: C, 59.13; H, 5.41; N, 12.54. Found: C, 59.09; H, 5.48; N, 12.52.

Conclusion

We have developed an efficient and practical large-scale process for the preparation of gefitinib with high purity (>99% by HPLC). The key step of the synthesis includes selective *O*-alkylation with significantly suppressed production of the *N*-alkylation product by using a transient TMS protecting group. Our process ultimately provided a significant improvement in both the yield and purity of the final gefitinib. We further confirmed that our procedure is applicable to a variety of anilinoquinazolines and can be widely utilized by synthetic and medicinal chemists.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant for the Global Core Research Center (GCRC) funded by the Korea government (MSIP) (No. 2011-0030001) and by the Global Frontier Project grant of National Research Foundation funded by Korea government (MSIP) (NRF-2015M3A6A4065798). We acknowledge the Korea Basic Science Institute, Ochang, Korea, for providing HRMS.

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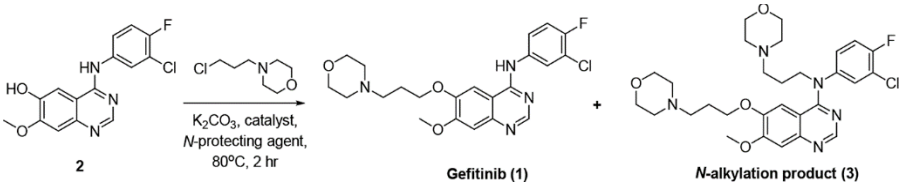
Table 1. *O*-alkylation of **2** with or without an assistance of TMSI as a transient protection group



2 Gefitinib (1) *N*-alkylation product (3)

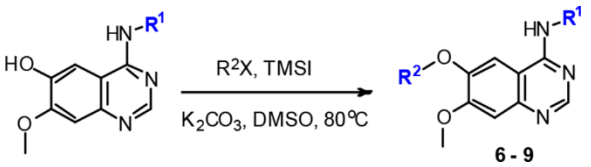
Entry	*N*-protecting agent	Catalyst	*N*-alkylation products before purification[a] (%)	*N*-alkylation products after purification[b] (%)	Yield[c] (%)
1	HCl	–	13.5	1.2	64.5
2	–	DMAP (0.1 eq.)	10.0	1.0	61.6
3	–	KI (0.1 eq.)	20.0	1.3	63.9
4	TMSI	–	2.2	0.2	78.5
5	TMSI	DMAP (0.1 eq.)	0.3	N.D.	90.1

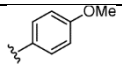
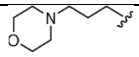
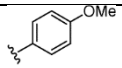
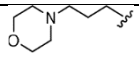
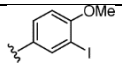
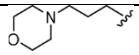
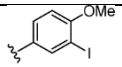
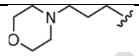
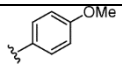
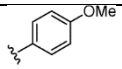
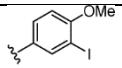
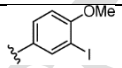
[a]Determined by HPLC after completion of reaction.

[b]Determined by HPLC after purification.

[c]Isolated yield after purification.

Table 2. Selective O-alkylation of 4-anilinoquinazoline moieties with an assistance of TMSI

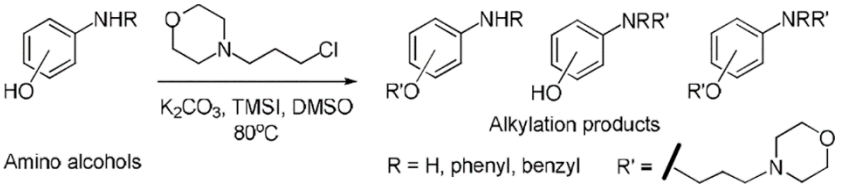


Entry	R^1	R^2	*N*-protecting agent	*N*-alkylation product[a] (%)	Yield[b] (%) (product)
1			–	23.2	64.5
2			TMSI	0.2	88.6 (**6**)
3			–	39.7	53.9
4			TMSI	1.3	83.5 (**7**)
5			–	30.6	54.4
6			TMSI	9.5	75.0 (**8**)
7			–	21.5	62.0
8			TMSI	4.4	80.2 (**9**)

[a]Determined by HPLC after completion of reaction.

[b]Isolated yield after purification.

Table 3. TMSI-assisted alkylation of amino alcohols



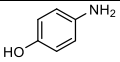
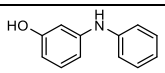
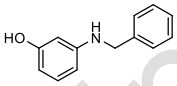
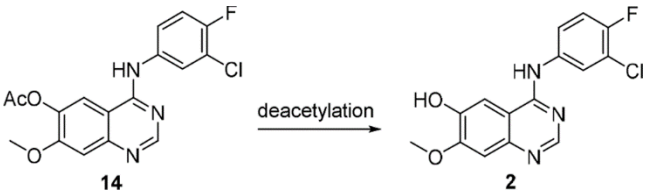
Amino Alcohol				
Major Product	*di*-alkylation product (**10**)	(**11**)	*O*-alkylation product (**12**)	*N*-alkylation product (**13**)
Isolated yield (%)	56.2	61.5	78.3	69.7

Table 4. Examination of deacetylation conditions for the preparation of intermediate **2**



14 **2**

Entry	Reagent	Temperature	Time (h)	Remaining **14**[a] (%)	Yield[b] (%)
1	NH_4OH	r.t. to reflux	18.5	2.0	90.5
2	NaOH	r.t.	1	0.1	90.2
3	KOH	r.t.	1	0.1	91.6
4	LiOH	r.t.	0.5	0.1	90.0

[a]Determined by HPLC after completion of reaction.

[b]Isolated yield.

Figure 1. Current drugs consisting of 4-anilinoquinazoline.

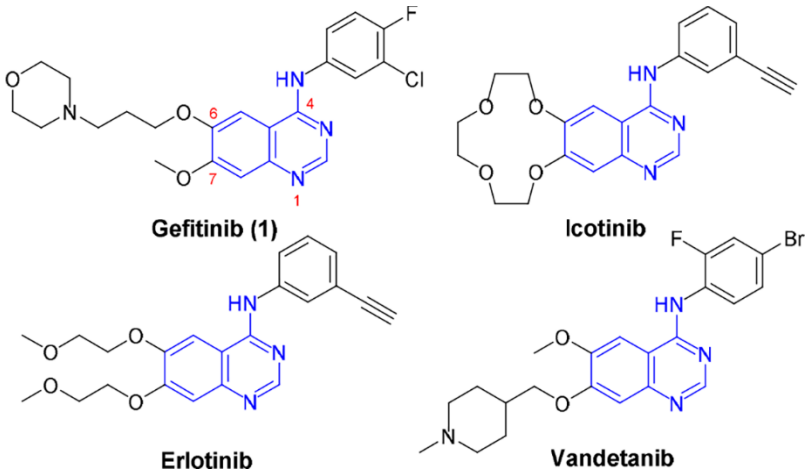


Figure 2. Strategy for the synthesis of 6-alkoxy quinazolines.

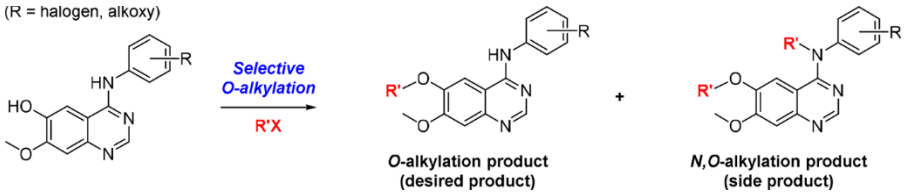
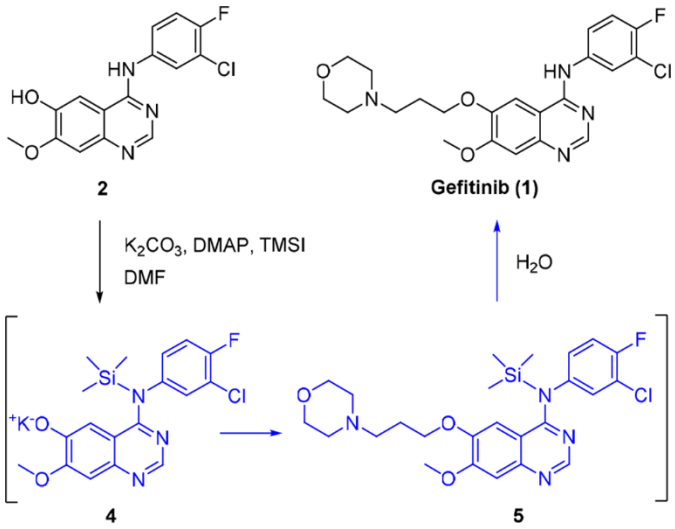


Figure 3. Postulated mechanism for selective *O*-alkylation of **2** using a transient protecting group.



Scheme 1. Synthesis of gefitinib (**1**).