

PROCESS FOR THE SYNTHESIS OF 6-AMINO-4-(3-CHLORO-4-FLUORO-PHENYLAMINO)-7-ETHOXY-QUINOLINE-3-CARBONITRILE

BACKGROUND OF THE INVENTION

5 The two most frequently used synthetic methods for the preparation of 3-cyano-4-quinolones or 3-carboalkoxyquinolones are intramolecular Friedel-Crafts reactions and electrocyclic ring closures of N-(2-carboxyvinyl)-aniline derivatives. Friedel-Crafts conditions work well for electron rich anilines, moderately for unsubstituted anilines, and poorly or not at all for electron-deficient anilines and are
10 not useful for large scale preparation of 3-cyano-4-quinolones especially utilizing electron deficient anilines. The electron withdrawing groups of the aniline reduce the nucleophilicity of the aromatic ring to the point that side reactions compete with, if not dominate, the desired intramolecular condensation.

 Thermal conditions for electrocyclic ring closures of N-(2-carboxyvinyl)-aniline
15 derivatives typically require temperatures in excess of 240°C. In U.S. Patent No. 6,002,008 the construction of 3-cyano-4-quinolones has been achieved by electrocyclic ring closure reactions of N-(2-carboxyvinyl) aniline derivatives by heating to 260°C in diphenyl ether. Thermal decomposition of either the final product and/or the starting material compromises the purity of the final product as a result of
20 the high temperature reaction conditions. Equipment necessary to perform high temperature reactions safely on larger scale is expensive and not available in a typical laboratory or plant environment. Typically, reactions are run at high dilution resulting in an inefficient large-scale process due to low throughput.

 The production of 3-cyano-4-quinolones by electrocyclic ring closure suffers
25 from all of the problems mentioned above. For example, it is known that 7-ethoxy-4-hydroxy-6-nitroquinoline-3-carbonitrile decomposes at 240°C while the minimum temperature required for cyclization is 256°C.

 There is a need for a process which overcomes the problem of thermal decomposition of intermediate compounds, including 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile used to epidermal growth factor
30 receptor (EGFR) inhibitors useful in the treatment of cancer.

The following experimental details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed to limit in any way the invention set forth in the claims that follow thereafter.

BRIEF SUMMARY OF THE INVENTION

- 5 This invention relates to producing 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile which comprises:
- 10 (a) acylating 2-Amino-5-nitrophenol with an acylating agent to obtain 2-Acetamido-5-nitrophenol;
- (b) alkylating 2-Acetamido-5-nitrophenol of step (a) with an alkylating agent in the presence of a base to obtain 4-Acetamide-3-ethoxynitrobenzene;
- 15 (c) reacting 4-Acetamide-3-ethoxynitrobenzene of step (b) to obtain 4-Acetamido-3-ethoxy-aniline;
- (d) condensing 4-Acetamido-3-ethoxy-aniline of step (c) with (ethoxymethylene)cyanoacetate to yield 3-(4-acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester;
- 20 (e) cyclizing 3-(4-Acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester of step (d) to yield 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline;
- 25 (f) reacting 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline of step (e) with a chlorine-substituting reagent to obtain 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline; and
- 30 (g) hydrolyzing 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline of step (f) with acid to yield 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile.;

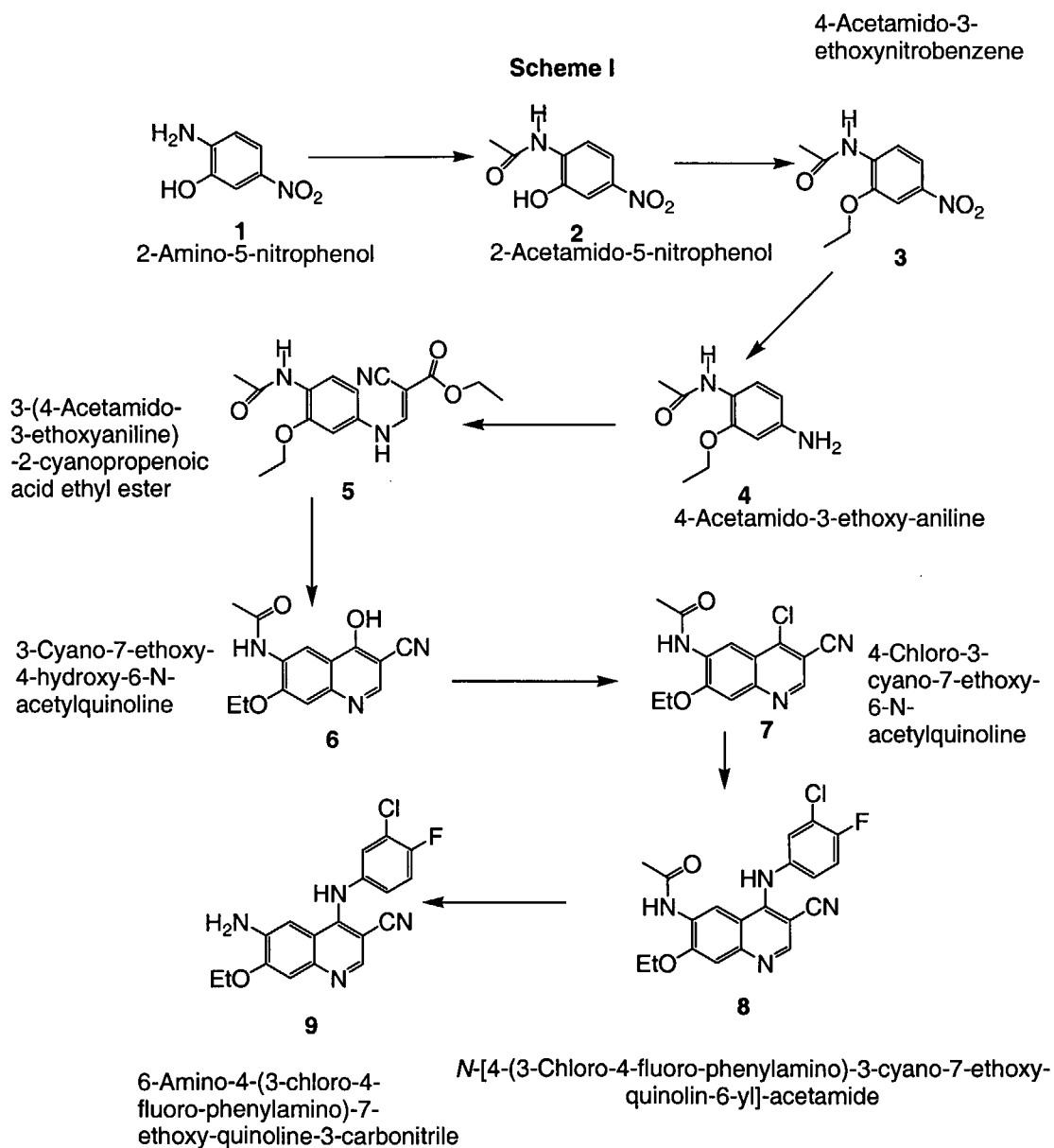
- (h) optionally converting 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile to a pharmaceutically acceptable salt form thereof.

5 Pharmaceutical acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this
10 invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, such as alkali metal salts (for example, sodium, lithium, or potassium) alkaline earth metal salts, ammonium salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, and trialkylammonium salts containing 1-6 carbon atoms in each
15 alkyl group, when a compound of this invention contains an acidic moiety.

 In accordance with this invention there is provided the following compounds and a process for the synthesis of 2-Acetamido-5-nitrophenol; 4-Acetamido-3-ethoxynitrobenzene, 3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic acid ethyl ester, 4-acetamido-3-ethoxy-aniline, 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline, 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline, and 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile.
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DETAILED DESCRIPTION OF THE INVENTION

A preferred process of the invention is shown in Scheme I:



The acetylation of 2-Amino-5-nitrophenol **1** is performed by adding an acylating agent at 60 °C to a stirred suspension of 2-Amino-5-nitrophenol and acetic acid to yield 2-Acetamide-5-nitrophenol **2**.

The alkylation of 2-Acetamido-5-nitrophenol **2** is performed by adding an alkylating reagent to yield 4-Acetamido-3-ethoxynitrobenzene **3**.

4-Acetamido-3-ethoxynitrobenzene **3** in tetrahydrofuran (10 parts) is reduced to 4-Acetamido-3-ethoxy-aniline **4** under hydrogenation conditions (10% Pd/C wet, 50 psi, 2 hours). The concentrate is condensed by dilution with toluene and reaction with commercially available ethyl (ethoxymethylene) cyanoacetate at reflux for 16
5 hours. After the reaction reaches completion, the mixture is cooled. The precipitated product is collected by filtration, washed and dried to yield 3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic acid alkyl ester **5**.

3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic acid ethyl ester **5** is cyclized in a solvent at a temperature of about 230-258 °C (in a preferred
10 embodiment the temperature was 250 °C) to yield 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline **6**.

3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline **6** is reacted with a chlorine-substituting reagent to yield 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline **7** followed by condensation with 3-chloro-4-fluoroaniline optionally in the presence of
15 acid to yield N-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-acetamide **8**.

N-[4-(3-Chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-acetamide **8** is hydrolyzed with acid to yield 6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile **9**.

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Example 1

2-acetamido-5-nitrophenol

Acetic anhydride (398 g, 3.90 mol) was added to a stirred suspension of 2-amino-5-nitro-phenol (400 g, 2.60 mol) and acetic acid (1.60 L) at 62.5°C. The reaction mixture was stirred at 62.5°C for 1 hour, and then cooled to room
25 temperature. Water (2.00 L) was added over 20 minutes to the stirred reaction mixture. After stirring for 1 hour, the solid was collected by vacuum filtration and washed with water and heptane. Drying the product *in vacuo* at 60°C yielded 486.7 g (96%, 99.5% by HPLC) of N-(2-hydroxy-4-nitro-phenyl)-acetamide. ¹H NMR (DMSO-d₆) δ (ppm) 2.18 (s, 3H), 7.70 (m, 2H), 8.30 (d, 1H), 9.45 (s, 1H), 11.00 (s, 1H).

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Example 2

2-Acetamido-5-nitrophenol

A 5-L multi-necked flask equipped with a mechanical stirrer, reflux condenser, nitrogen inlet, 500-mL addition funnel, heating mantle, and a thermocouple attached to a temperature controller was charged with 400 g 2-Amino-5-nitrophenol. The flask was then charged with 1.6 L of acetic acid. The resulting mixture was stirred and warmed to 60 ± 2 °C to achieve a suspension. While maintaining the temperature at 62.5 ± 2.5 °C 398 g of acetic anhydride was added over 1.5 hours and stirred for one hour to 2-Acetamido-5-nitrophenol with less than 1% of 2-Amino-5-nitrophenol present. If necessary 37 mL of acetic acid was added to reduce the concentration of 2-Amino-5-nitrophenol. The reaction mixture was cooled to 20 ± 5 °C and 2.00 L of water was added over 20 minutes and the suspension was stirred for one hour. Using vacuum filtration the suspension containing 2-Acetamido-5-nitrophenol was collected, washed with water followed by a heptane wash, and dried in a vacuum. Yield 486.7 g (96%), strength 101.2%, mp >250 °C, ¹HNMR (DMSO d₆) δ 1.42 (t, 3H), 2.20 (s, 3H), 4.25 (q, 2H), 7.78 (d, 1H), 7.78 (dd, 1H), 8.36 (d, 1H), 9.42 (s, 1H).

Example 3

4-Acetamido-3-ethoxynitrobenzene

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A 12-L, 4-necked flask equipped with a reflux condenser, nitrogen inlet, thermocouple, addition funnel, and mechanical stirrer was charged with 400 g 2-Acetamido-5-nitrophenol. The flask was charged with 790 g potassium carbonate and 2.0 L of dimethylformamide (DMF). The mixture was stirred and warmed to 60 ± 2.5 °C. 294 g of ethyl bromide or ethyl iodide was added over 10 minutes to one hour while maintaining a 60°C internal temperature. The reaction mixture was stirred for at least one hour or until the mixture turned yellow and the concentration of 2-Acetamido-5-nitrophenol was less than 1%, if needed additional ethyl bromide or ethyl iodide or ethyl chloride was added to reduce the concentration of 2-Acetamido-5-nitrophenol present. The mixture was cooled to 20 ± 5 °C. 4 L of water was added and while maintaining a 25 ± 5 °C internal temperature. The suspension was stirred for a minimum of 30 minutes and collected by vacuum filtration. The product was washed and the pH monitored for a pH of < 8. If the pH was > 8, the product was washed with 1.0 L portions of warm water until the pH was < 8. The resultant

product was washed with heptane and vacuum dried. Yield 98%, strength 98.6%, mp 164-165°C.

Example 4

3-(4-Acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester

5 A 2- gallon Parr #2 hydrogenator was purged with nitrogen and charged with 10% palladium on carbon and 4-Acetamido-3-ethoxynitrobenzene. The closed reactor was purged an additional 3 times with nitrogen and tetrahydrofuran (THF) was added from a pressure bomb. The reactor was purged an additional 3 times with nitrogen and 3 times with hydrogen and the reaction mixture was hydrogenated
10 at 50 psi at 28-30°C for 3 hours using an uptake meter. After completion the reaction mixture was filtered and rinsed with THF. A 6 L multi-neck flask with a mechanical stirrer, thermometer, still head for reduced pressure distillation, condenser, and receiver was charged with the filtrate using a THF rinse. The solution was concentrated, filtered, and washed with toluene. The filtrate was stirred with toluene
15 and ethyl(ethoxymethylene)cyanoacetate and heated to reflux of 90°C with stirring for 16 hours. The product was filtered and washed with toluene and dried with a vacuum to yield 3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic ethyl ester. Yield 534.0 g, 90.3%, ¹H NMR (DMSO- d₆) δ1.25 (m, 6H), 1.38 (t, 6H), 2.10 (s, 3H), 3.35 (s, 3H), 4.05-4.30 (m, 8H), 6.95 (t, 2H), 7.10 (s, 1H), 7.25 (s, 1H), 7.85 (d, 2H), 8.30
20 (d, 2H), 8.50 (d, 2H), 9.00 (s, 2H), 10.70 (d, 2H).

Example 5

3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline

A 22 L 4-necked flask equipped with a reflux condenser, nitrogen inlet, two
25 thermocouples attached to two independent temperature controllers, and a mechanical stirrer was charged with 210 g of 3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic acid ethyl ester. The flask was charged with 12.0 L of Dowtherm A. A nitrogen flow was introduced over the reaction, venting through the condenser. The mixture was stirred and warmed to 250 ± 5°C while maintaining the temperature
30 and monitoring the reaction by high performance liquid chromatography (HPLC) to obtain > 49 % (relative area) 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline. The reaction mixture was cooled to room temperature. The solid was collected by filtration and washed with toluene. In a 2-L 4-necked flask, equipped with a water-

cooled condenser, overhead stirring apparatus and N₂ blanket the solid and THF were collected. The mixture was stirred and warmed to reflux and maintained for a minimum of 30 minutes. The resultant mixture was cooled to room temperature, collected by filtration, washed with THF and vacuum dried to yield 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline. Yield 42%, strength 95.2%, mp >250 °C, ¹H NMR (DMSO-d₆) δ 1.42 (t, 3H), 2.15 (s, 3H), 4.21 (q, 2H), 7.08 (s, 1H), 8.60 (s, 1H), 9.17 (s, 1H), 12.50 (s, 1H)

Example 6

4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline

A 2-L 4-necked flask with a water-cooled condenser, thermal probe connected to a temperature controller, heating mantle, nitrogen blanket, and overhead stirrer was charged with 80 g of 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline. The flask was charged with 1.6 L of diethylene glycol dimethyl ether or dioxane and stirred. The flask was charged with 96.0 mL of phosphorus oxychloride and warmed to 100 ± 2°C and maintained for 45 minutes. HPLC was used to verify that < 1% (relative area) 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline remained in the reaction mixture. The mixture was cooled to 80 ± 5°C and 25 g celite was added. The reaction mixture was filtered and the flask and celite were washed with 3x100 mL and 1x50 mL diethylene glycol dimethyl ether.

The volume of the filtrate was reduced using a vacuum. The concentrated filtrates were added to a stirred aqueous solution of 70 g of K₂CO₃ in water while maintaining a temperature of < 50°C. The solid was collected by filtration and washed with warm water and toluene and vacuum dried to yield 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline. Yield 65%, strength 82%, mp 250 °C, ¹H NMR (DMSO-d₆ + CDCl₃) δ 1.45 (t, 3H), 2.20 (s, 3H), 4.30 (q, 2H), 7.10 (m, 1H), 7.15-7.40 (m, 3H), 8.50 (s, 1H), 8.85 (s, 1H), 9.20 (s, 1H), 9.60 (s, 1H)

Example 7

N-[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinoline-6-yl]-acetamide

A stirred mixture of N-(4-chloro-3-cyano-7-ethoxy-6N-acetylquinoline (274.5 g, 0.947 mol), 3-chloro-4-fluoroaniline (180 g, 1.24 mol), methanesulfonic acid, (5.5 g, 0.057 mol), and 2-propanol (6.7 L) was warmed to reflux (84°C) for 6.5 hours.

After stirring overnight at room temperature, the mixture was warmed to 80°C. Water (3.2 L) containing concentrated hydrochloric acid (655 mL of 38% aqueous HCl) was added. The reaction was kept at reflux for 5 hours. The reaction mixture was cooled to 0°C-10°C for 1 hour. The yellow solid product was collected by vacuum filtration and washed with 20 % 2-propanol/water (700 mL) and water (2x700 mL). Drying the product *in vacuo* at 60°C gave 344.8 g (91%, 99 % by HPLC) of 6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile as a hydrochloride salt. ¹H NMR (DMSO-d₆ + D₂O) δ1.42 (t, 3H), 4.25 (q, 2H), 7.05 (m, 1H), 7.1 (s, 1H), 7.35-7.50 (m, 3H), 7.65 (dd, 1H), 8.65 (s, 1H).

Example 8

6-Amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile

Aqueous potassium carbonate (1.0 L of 10%, 0.725 mol) was added over 30 minutes to 45 minutes to a stirred suspension of 4-(3-chloro-4-fluoroanilino)-3-cyano-7-ethoxy-6-aminoquinoline (HCl salt, 391 g, 1.00 mol), methanol (3.90 L), and water (0.90 L) maintained at 65°C. Water (1.0 L) was then added over 15 minutes. The reaction mixture was allowed to cool to room temperature and stirred overnight. The reaction mixture was cooled to 0°C – 5°C for 30 minutes. The solid product was collected by vacuum filtration. The solid was washed with water (3x100 mL, 50°C – 55°C). Drying the product *in vacuo* at 60°C gave 344.7 (97 %, 99.2 % by HPLC) of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile. ¹H NMR (DMSO-d₆) δ1.42 (t, 3H), 4.25 (q, 2H), 5.55 (broad s, 2H), 7.05 (m, 1H), 7.2-7.3 (m, 3H), 7.38 (t, 1H), 8.4 (s, 1H), 9.22 (broad s, 1H); ¹³C NMR (DMSO-d₆) δ15.09, 64.72, 91.78, 101.46, 108.43, 117.14, 117.57, 117.85, 118.16, 120.33, 121.52, 122.72, 140.05, 145.28, 148.02, 152.31, 155.55.

For purposes of this invention an acylating agent is for example acetic anhydride, halide, alkyl and acetyl chloride.

For purposes of this invention an alkylating agent includes ethyl iodide, ethyl bromide or ethyl chloride in an inert solvent such as N,N-dimethylformamide or DMSO, dimethylacetamide, acetone, or any ketone.

For purposes of this invention a base includes alkali metal hydroxides, alkali metal acetates, pyridine, 4-dimethylaminopyridine, sodium carbonate, inorganic carbonates and potassium carbonate.

5 For purposes of this invention a reducing agent includes iron and ammonium chloride, sodium dithionite in an aqueous medium, and hydrogen assisted by metal catalysis with metals such as palladium and platinum dispersed on carbon or another inert support.

10 For purposes of this invention a solvent includes benzene, toluene, acetonitrile, diphenyl ether, or tetrahydrofuran (THF). In a preferred embodiment the solvent is a mixture of biphenyl and diphenyl ether.

For purposes of this invention a chlorine-substituting reagent includes
15 phosphorous oxychloride and phosphorous pentachloride neat or in an inert solvent such as THF, dioxane, oxalyl chloride, thionyl chloride or 1,2-dimethoxyethane.

For purposes of this invention an acid includes hydrochloric acid, sulfuric acid, methanesulfonic acid, alkanesulfonic acids in general, *p*-toluenesulfonic acid,
20 benzenesulfonic acid, mineral acids as for example hydrochloric acid, or arylsulfonic acids in general.

WHAT IS CLAIMED IS:

1. A compound consisting of 3-(4-Acetamido-3-ethoxyaniline)-2-cyanopropenoic acid ethyl ester.
2. A compound consisting of 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline.
- 5 3. A compound consisting of 4-Chloro-3-cyano-7-ethoxy-6-N-acetylquinoline.
4. A compound consisting of N-[4-(3-chloro-4-fluoro-phenylamino)-3-cyano-7-ethoxy-quinolin-6-yl]-acetamide.
5. A compound consisting of 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile.
- 10 6. A compound consisting of 4-Acetamido-3-ethoxy-aniline.
7. A compound consisting of 2-Acetamido-5-nitrophenol.
8. A compound consisting of 2-Acetamido-3-ethoxynitrobenzene.
9. A process of making 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile which comprises:
 - 15 (a) cyclating 2-Amino-5-nitrophenol with an acylating agent to obtain 2-Acetamido-5-nitrophenol;
 - (b) alkylating 2-Acetamido-5-nitrophenol of step (a) with an alkyl halide in the presence of a base to obtain 4-Acetamide-3-ethoxynitrobenzene;
 - (c) reducing 4-Acetamide-3-ethoxynitrobenzene of step (b) to obtain 4-Acetamido-3-ethoxy-aniline;
 - 20 (d) condensing 4-Acetamido-3-ethoxy-aniline of step (c) with ethyl(ethoxymethylene)cianoacetate to yield 3-(4-Acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester;
 - (e) cyclizing 3-(4-Acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester of step (d) to yield 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline;
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- (f) reducing 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline of step (e) with a chlorine-substituting reagent to obtain 4-Chloro-3-cyano-7-ethoxy-3-quinolincarbonitrile; and
- (g) hydrolyzing 4-Chloro-3-cyano-7-ethoxy-3-quinolincarbonitrile of step (f) with acid to yield 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile or the salt thereof.
10. The process of claim 9 wherein the acylating agent in step (a) is acetic anhydride.
11. The process of claim 9 or 10 wherein the alkylating agent in step (b) is ethyl bromide.
12. The process of any one of claims 9 to 11 wherein the solvent in step (e) is a mixture of biphenyl and diphenyl ether at a temperature range of about 230-258 °C.
13. The process of claim 12 wherein the temperature is about 250 °C.
14. The process of any one of claims 9 to 13 wherein the chlorine-substituting reagent in step (f) is phosphorous oxychloride.
15. The process of any one of claims 9 to 14 further comprising converting 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile to a pharmaceutically acceptable salt form thereof.
16. A process for the preparation of 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline by heating 3-(4-Acetamido-3-ethoxyaniline)-2-cyano-propenoic acid ethyl ester.
17. The process of claim 16 further comprising converting 3-Cyano-7-ethoxy-4-hydroxy-6-N-acetylquinoline to 6-amino-4-(3-chloro-4-fluoro-phenylamino)-7-ethoxy-quinoline-3-carbonitrile or a pharmaceutically acceptable salt form thereof.