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Safe and Practical Large-Scale Synthesis of 2-Aminoquinoline-6-Carboxylic Acid Benzyl Ester

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Abstract:

An efficient three-step sequence has been developed for the synthesis of 2-aminoquinoline-6-carboxylic acid benzyl ester starting from commercially available 6-quinolinecarboxylic acid. The process features a novel and exceptionally mild conversion of a quinoline *N*-oxide to a 2-aminoquinoline using a triethylamine/ammonium chloride buffered system. The development of this procedure is especially important since gaseous ammonia, ammonium hydroxide, and solutions of ammonia in alcohols all failed to deliver a safe and reliable process.

Introduction

In a recent development program of a drug candidate, we required multi-kilogram quantities of 2-aminoquinoline-6-carboxylic acid as an ester derivative. A straightforward approach, which would provide direct entry to the 2-aminoquinoline core structure, lies in a vicarious amination of commercially available 6-quinolinecarboxylic acid (**1**). Although the corresponding Chichibabin reaction has been reported in earlier literature, the exact regioselectivity of the aminoquinoline carboxylic acid produced was not established.[1] Moreover, the reaction conditions using potassium amide under a sealed vessel raised safety concerns and were deemed not amenable to large-scale preparation. Alternatively, conversion of quinoline *N*-oxides to the 2-aminoquinolines could provide a means to effect the desired transformation.[2] Hence, the original discovery synthesis was developed based on this approach, and initial assessment of the procedures employed raised several process related issues. More specifically, 6-quinolinecarboxylic acid (**1**) is first derivatized as the oily *tert*-butyl ester (**2**) via the *tert*-butyl alcohol adduct **3** of diisopropylcarbodiimide (Scheme 1).[3] The latter is also an oily substance that is freshly prepared and used crude in the process. Of particular concern is the subsequent oxidation to the *N*-oxide **4**, which has the potential to be a highly energetic compound. The procedure also utilizes corrosive trifluoroacetic anhydride.[4] The following amination protocol leading to the 2-aminoquinoline **5** employs chloroform as a solvent and also produces the corresponding 2-hydroxyquinoline **6** as a major byproduct.[5] Herein, we report our efforts to address these very issues to develop a safe and scalable process of the title compound **5**.

Results and Discussion

One of our first goals was to identify a derivative of 6-quinolinecarboxylic acid that would impart crystallinity and avoid the separate preparation of diisopropylcarbodiimide/*tert*-butyl alcohol adduct **3**. Although the methyl and ethyl esters have been previously synthesized, the corresponding 2-amino derivatives were poorly soluble and caused difficulties in the downstream chemistry. The working hypothesis was that the lipophilic nature of the *tert*-butyl ester increased the solubility, so we reasoned that a benzyl ester would behave similarly. Such a derivative would also offer the choice of either cleavage by hydrogenolysis or saponification in the later stage of the synthesis. This was especially important since we needed to commit early to meet the deadlines before the removal of the protecting group could be assessed. Hence, the benzyl ester **7** was prepared using CDI in ethyl acetate and was found to be a crystalline intermediate, avoiding the chromatographic step (Scheme 2). The scale-up went as planned except that the acylimidazole intermediate crystallized out of solution on scale. Although this event did not occur on laboratory scale, crystallization was of no consequence to the reaction outcome. The yield of the benzyl ester **7** was 6.45 kg (94%).

With the benzyl ester **7** in hand, the *N*-oxidation was then investigated using the original discovery procedure to secure material for safety assessment. Results from DSC testing on the *N*-oxide **8** showed decomposition with an onset temperature of 168 °C with an energy release of 596 J/g, classifying it as a high thermal potential. ARC results indicated that the material has a corrected onset of 137 °C with a time to maximum rate of greater than a month at the maximum process temperature. Based on these results, the *N*-oxide **8** was deemed safe to handle at room temperature. Since the original process utilized trifluoroacetic anhydride, we investigated the use of a less corrosive agent and found that phthalic anhydride,[6] which comes as a free-flowing solid, also gave yields greater than 90% when performed in dichloromethane or THF. Although the conversion was not

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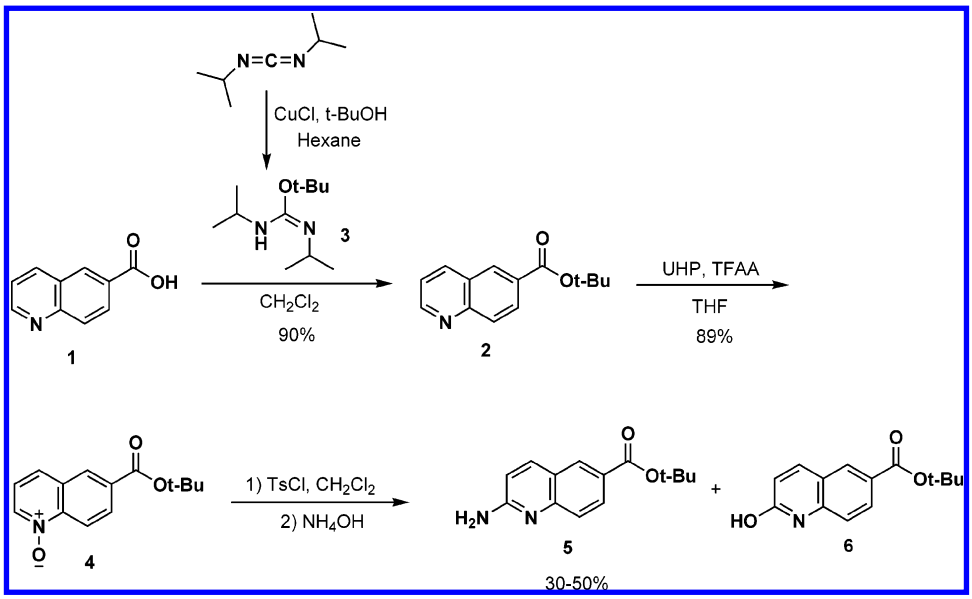
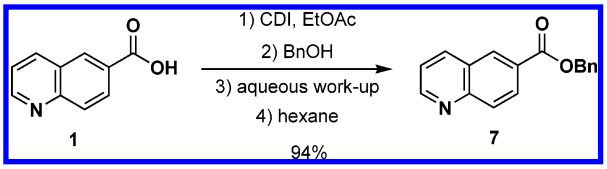
Scheme 1



an issue, the workup and isolation were more problematic as it produced some emulsions. Since these were manageable on a 100 g scale, we focused on the scale-up.

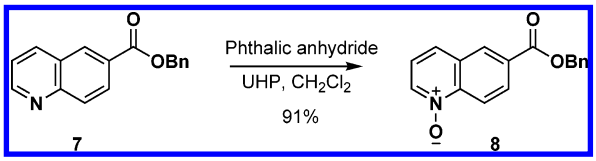
Scheme 2



Complete conversion of the benzyl ester **7** to the *N*-oxide **8** in the first scale-up was readily achieved in approximately 24 h, but the workup caused major difficulties. More specifically, once the reaction mixture was quenched in aqueous sodium thiosulfate/hydrochloric acid and the phases were separated, subsequent treatment of the organics with aqueous sodium bicarbonate led to a stable emulsion. In an effort to achieve separation, the mixture was diluted with more water and left to settle overnight. At this stage, the phases were separated, but since some emulsion still remained at the interface, the aqueous layer was treated with brine and back-extracted twice with additional methylene chloride at 35 °C, again allowing it to settle overnight. The combined organic layers, in which some emulsions remained, were concentrated and then replaced with ethyl acetate. The mixture was further concentrated under partial vacuum with concomitant azeotropic removal of water and then cooled once the solution was anhydrous with a final volume of 3.5 L/kg (with respect to the starting material). Once 4.3 L/kg of hexane was added as antisolvent, the solids were isolated by filtration and dried to yield 4.1 kg of desired *N*-oxide **8** contaminated with 9.5% of ashes. The lower than expected yield of 90% and the presence of inorganic material were due to the emulsions encountered in the process.

In a subsequent *N*-oxidation run, the typical emulsion was observed during treatment of the dichloromethane layer with aqueous sodium bicarbonate. Since the dichloromethane is to be replaced by ethyl acetate after all the extractions are complete, we decided to investigate whether this solvent swap could be accomplished earlier on to avoid the emulsion. We found that such an operation had no deleterious impact on the *N*-oxide **8** and that a clean phase separation was achieved once the dichloromethane had been replaced with ethyl acetate. As an added benefit, the material produced in this process contained no ashes. The overall yield for this run was 91% (Scheme 3).

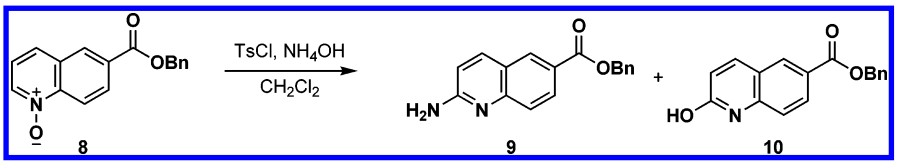
Scheme 3



It soon became apparent that conversion of the *N*-oxide **8** to the amine **9** was a major challenge. We first assessed the original discovery procedure with the exception that chloroform was replaced with dichloromethane. Hence, the *N*-oxide **8** was treated with tosyl chloride, followed by the addition of ammonium hydroxide. Upon reaction completion, the organics were concentrated and the residual material was triturated in ethyl acetate. Unfortunately, our product was contaminated with the corresponding 2-hydroxyquinoline **10**, which required several triturations to ensure its removal. In our hands the yield was only 10% (Scheme 4).

We next assessed the effect of various solvents on the reaction outcome. Since we had originally substituted chloroform by dichloromethane, we next performed a side-by-side comparison and found that dichloromethane was a superior solvent since it did not produce the major dimer impurity **11** found in the chloroform reaction. While the use of 1,2-dichloroethane produced similar results to the dichloromethane, there were no significant advantages. Switching to THF, the reaction cleanly produced yet another new product characterized as tosylamide. In this solvent system, the *N*-oxide was presumably not undergoing sulfonylation with tosyl chloride. We hypothesized that the initial sulfo-

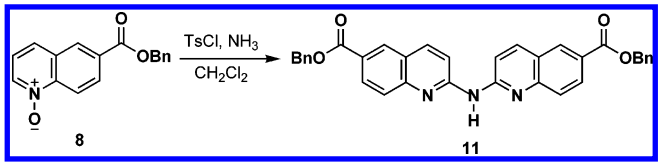
Scheme 4



nylation of the *N*-oxide **8** by tosyl chloride was in equilibrium with the desired tosylated *N*-oxide species. If this were the case, then switching to a less nucleophillic counterion by using tosic anhydride should increase the conversion, but this reaction led to an intractable mixture. We therefore chose to run all future experiments with tosyl chloride in dichloromethane and focus our efforts on different ammonia sources.

As mentioned above, the use of ammonium hydroxide as source of ammonia led to a 1:1 mixture of 2-amino (**9**) and 2-hydroxyquinoline (**10**) in approximately 40% yield. Since the presence of water was the culprit, we performed a reaction using ammonia gas, which led almost exclusively to dimer **11** (Scheme 5). In this particular case, the 2-aminoquinoline product **9** was sufficiently active to react with the tosylated *N*-oxide in the ammonia-starved environment during the gassing procedure.

Scheme 5



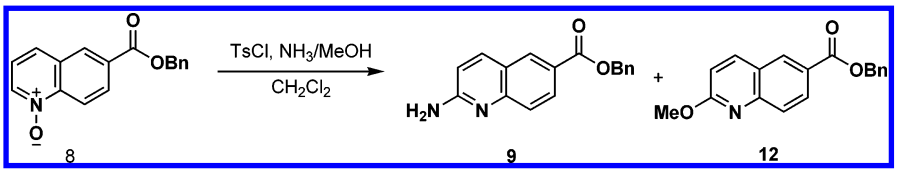
We then switched to alternative commercially available ammonia solutions (1 M in methanol and 2-propanol). As compared to water, we were hoping that the increased steric hindrance of methanol and 2-propanol would decrease their competitive addition pathways. This indeed was the case with methanol, whereas the 2-propanol solution led to an intractable mixture. At this time, we found that the desired 2-aminoquinoline **9** was relatively insoluble in a more concentrated reaction mixture in dichloromethane/methanol. This was an especially important finding since the product could be isolated directly from the reaction mixture by simple filtration and no longer required multiple reslurries in ethyl acetate. The success of this reaction, however, was dependent on the rate of addition of the ammonia solution. More specifically, the ammonia solution must be added at a fast rate; otherwise the reaction mixture becomes starved of NH_3, and MeOH then acts as a nucleophile. In fact, the 2-methoxyquinoline **12** was formed almost exclusively when the addition was performed dropwise. The issue with respect to a fast addition rate lied in the high amount of energy released in the reaction. For example, when the ammonia solution in methanol was added at once, an exotherm of 40 °C was observed. In an effort to avoid a sudden release of energy, we reasoned that an inverse addition of the activated species to the ammonia solution would allow a slow addition rate since the reaction mixture would not be starved of ammonia.[2a] Unfortunately, this mode of addition only provided a 5% yield of 2-aminoquinoline **9**. Presumably, the higher concentration of ammonia led to amidation of the benzylic ester. Besides the exotherm issue, the rapid addition procedure did prove reliable in consistently providing a 50−60% yield of 2-aminoquinoline **9**.

Since the *N*-oxide **8** produced in the first run contained inorganic material, a Celite filtration was implemented prior to the activation with tosyl chloride. Once this was achieved, the solution of the tosylated intermediate was cooled to −10 °C to which a precooled solution of ammonia in methanol at −10 °C was rapidly added. Such a rapid addition was required to minimize competing nucleophilic addition of the solvent. In this context, the reaction temperature increased to 37 °C in a few minutes with minimal reflux in the condenser. At this stage, 2-aminoquinoline **9** crystallized out of solution and, upon cooling to −5 °C, could be directly isolated from the reaction mixture by simple filtration (Scheme 6). As this material contained some inorganics, the wet cake was reslurried in water, filtered, and washed with methanol to yield 216 g (52%) after drying.

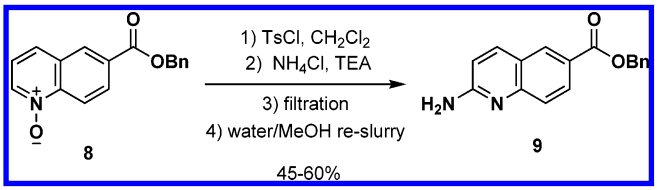
Safety assessment of the foregoing procedure was performed and was deemed unsafe to run on a larger than 25 L scale due to the large amount of off gassing during the process. After a series of failed attempts to solve this issue, a superior alternative was found by the in situ generation of ammonia from ammonium chloride and triethylamine. This buffered system now allows a successful inverse addition of the activated *N*-oxide to the ammonia source, whereas such an addition mode into ammonia solutions led to poor yields (vide supra). This set of reaction conditions is devoid of any nucleophilic solvent like water and methanol and provides similar yields to those of the previous method, and more importantly, the heat of the reaction can now be controlled by a slow rate of addition of the activated *N*-oxide to the suspension of ammonium chloride in TEA/dichloromethane.[7] Pilot scale experiments on a 100 g scale provided the desired compound in 65% yield. With the safety issues associated with the amination procedure resolved, scale-up was undertaken where a solution of *N*-oxide **8** in 4 volumes of methylene chloride was treated with tosyl chloride, and this solution was then slowly added to an ammonium chloride suspension in dichloromethane and triethylamine. An addition rate of approximately 500 mL/min was required to maintain a temperature range of 20 to 25 °C. The reaction mixture was stirred an additional hour, then cooled to −10 °C, and further stirred for 1.5 h and filtered. To remove triethylammonium chloride from the isolated solids, the product wet-cake was repulped in water, refiltered, and washed with methanol cooled at −10 °C. After drying under vacuum at 35 °C, 1.85 kg (45% yield) of desired 2-amino-

(7) It is noteworthy that the nature of the suspension is ammonium chloride and not triethylammonium chloride prior to the addition of the activated *N*-oxide solution.

Scheme 6



Scheme 7



quinoline **9** were isolated (Scheme 7). It is noteworthy that the filtrate originating from the reaction mixture also contained 15 to 20% of the desired product. Since the total amount of aminoquinoline was enough to support development activities, and due to the convenience of isolating the product directly from the reaction mixture, the matter of isolating additional 2-aminoquinoline **9** from the filtrate was not pursued at the time.

Concluding Remarks

This work demonstrates a safe and practical large-scale synthesis of 2-aminoquinoline **9**, where all the intermediates are crystalline solids. The process features an exceptionally mild conversion of a quinoline *N*-oxide to a 2-aminoquinoline using a triethylamine/ammonium chloride buffered system. The development of this procedure was especially important since gaseous ammonia, ammonium hydroxide, and solutions of ammonia in alcohols all failed to deliver a safe and reliable process. The synthesis described herein has successfully provided multi-kilogram quantities of **9** for use in the preparation of a drug candidate in a safe and timely manner. As the manufacturing requirements increase, efforts are underway to further improve the process for future campaigns.

Experimental Section

Unless otherwise noted, all the operations were performed in nitrogen purged vessels. All charges and transfers are performed using an isolated vacuum whenever possible. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Innova 400 spectrometer. Melting points were obtained from a Thomas-Hoover Uni-Melt capillary apparatus and are uncorrected.

Quinoline-6-carboxylic Acid Benzyl Ester (7). To a solution of 6-quinolinecarboxylic acid (**1**) (4.5 kg, 26 mol) in ethyl acetate (45 L) was added 1,1′-carbonyldiimidazole (4.64 kg, 28.6 mol). After stirring at 20−25 °C for 4 h, benzyl alcohol (2.95 kg, 27.3 mol) was added and the reaction mixture was stirred for 12 h at 20−25 °C. The reaction was quenched with a solution of concentrated HCl (4.4 L) in water (22 L). The phases were separated, and the aqueous layer was extracted with ethyl acetate (13.5 L). The combined ethyl acetate layers were washed with a solution of sodium bicarbonate (1.2 kg) in water (13.2 L) followed by a brine wash (3 kg of NaCl in 12 L of water). The ethyl acetate layer was concentrated by vacuum distillation to about 10 L, and hexane (20 L) was added at the rate 4 L/min until the solids began to precipitate, at which point the rate was reduced to 2 L/min. The resulting suspension was stirred for 1 h at 20−25 °C and slowly cooled to 0−3 °C and held for 4 h before filtering the solid product. The product was dried in a vacuum oven at 35−40 °C for 24 h to yield 6.45 kg (94.2%) of the title compound; mp 46−48 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (m, 1H), 8.60 (s, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.50−7.30 (m, 5H), 5.42 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.16, 152.79, 150.33, 137.58, 136.04, 131.37, 130.06, 129.26, 128.91, 128.80, 128.67, 128.57, 128.50, 128.30, 127.62, 122.10, 67.36. HRMS calcd for $C_{17}H_{14}NO_2$ (M + H^+), 264.1025; found, 264.0095.

1-Oxy-quinoline-6-carboxylic Acid Benzyl Ester (8). To a mixture of urea hydrogen peroxide (1.67 kg, 17.8 mol), phthalic anhydride (2.19 kg, 14.6 mol), and methylene chloride (41.2 L) was added to quinoline-6-carboxylic acid benzyl ester (**7**) (2.75 kg, 10.4 mol) under nitrogen. After stirring for 12 h at 20−25 °C, a solution of sodium thiosulfate pentahydrate (3.4 kg, 13.7 mol) in water (27.5 L) was added. After stirring for 30 min, a solution of concentrated HCl (1.2 L) and water (26.3 L) was added. The layers were separated, and methylene chloride (27.5 L) was added to the aqueous layer for a second extraction. A solution of sodium bicarbonate (1.4 kg) in water (44 L) was added to the combined methylene chloride layers. The heterogeneous mixture was stirred for 15 min, and the methylene chloride was removed by atmospheric distillation. Upon complete removal of methylene chloride, ethyl acetate (40 L) was added and the mixture was stirred for 15 min. The layers were separated, and the ethyl acetate solution was concentrated by vacuum distillation to about 10 L. The solution was cooled to room temperature until crystals form and hexane (12 L) was slowly added over 20 min. The suspension was cooled to 5−10 °C and held at that temperature for 4 h before filtering the solids. The product was dried in a vacuum oven at 35−40 °C for 24 h to yield 2.64 kg of the title compound (90.6%); mp 99−102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (d, J = 9.0 Hz, 1H), 8.63 (s, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.49−7.34 (m, 5H), 5.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.37, 143.55, 137.40, 135.66, 131.35, 130.68, 130.18, 128.97, 128.84, 128.80, 128.78, 128.72, 128.69, 126.85, 122.15, 120.69, 67.74. HRMS calcd for $C_{17}H_{14}NO_3$ (M + H^+), 280.0974; found, 280.0968.

2-Amino-quinoline-6-carboxylic Acid Benzyl Ester (9). To a solution of 1-oxy-quinoline-6-carboxylic acid benzyl ester (**8**) (4.1 kg, 14.7 mol) in methylene chloride (20 L)

was added *p*-toluenesulfonyl chloride (3.9 Kg, 21 mol) under nitrogen, and the mixture was stirred for 45 min at 22−25 °C. This solution was added very slowly (400 mL/min) to a suspension of ammonium chloride (2.4 kg, 44 mol) in methylene chloride (12 L) and triethylamine (6.8 L, 48 mol) while keeping the temperature at 25−30 °C. The reaction mixture was stirred for an additional hour at 22−25 °C before cooling to −5 °C for 1 h and filtered. The filtered solids were rinsed with pre-cooled methanol (4.5 L) at −5 °C. This solid material was then triturated in water (45 L) for 20 min at 20−25 °C, filtered, and washed with precooled methanol (9 L) at −5 °C. The product was dried in a vacuum oven at 35−40 °C for 24 h to yield 1.85 kg (45.1%) of the title compound; mp 199−202 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (s, 1H), 8.18 (dd, J = 2.0 Hz, 9.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 7.0 Hz, 2H), 7.42−7.33 (m, 3H), 6.74 (d, J = 9.0 Hz, 1H), 5.39 (s, 2H), 4.97 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.59, 158.52, 150.61, 139.36, 136.36, 130.98, 130.12, 128.84, 128.46, 126.15, 124.35, 122.84, 112.55, 66.95. HRMS calcd for $C_{17}H_{15}N_2O_2$ ($M + H^+$), 279.1134; found, 279.1120.

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