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Using Potassium Carbonate to Scavenge Hydrogen Fluoride: A Scale-Up Process for Quantitative Production of (1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-(oxo-κO)-3-quinolinecarboxylato-κO3)difluoro−Boron

Xun Li* and Ronald K. Russell

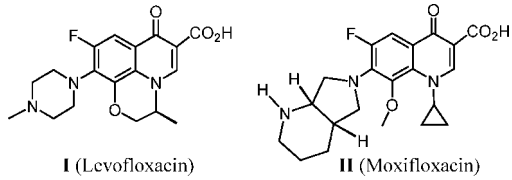
Johnson & Johnson Pharmaceutical Research & Development, L.L.C., East Coast Research & Early Development, 1000 Route 202, Raritan, New Jersey 08869, U.S.A.

Abstract:

Hydrogen fluoride is a byproduct from the reaction of treating 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4, 1.0 equiv) with borontrifluoride etherate (1.15−1.35 equiv) in refluxing THF solution. Scavenging the hydrogen fluoride evolved with potassium carbonate (1.15 equiv, 325 mesh) affords the desired (1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-(oxo-κO)-3-quinolinecarb-oxylato-κO3)difluoro−boron (5) in almost quantitative yield (>97%) with excellent chemical purity (≥99%). Hence, this reproducible and nonchromatographic process offers a benign method for large-scale (multikilogram) production of difluoro−boron complex 5.

Introduction

The synthesis of fluoroquinolinones has attracted the attention of medicinal chemists in the pharmaceutical industry due to their broad spectrum of activity against various bacteria, mycobacteria, and parasites.[1] Two well-known examples among the clinically used fluoroquinolinone antibiotics are levofloxacin (**I**)[2] and moxifloxacin (**II**).[3] Structural analysis of compounds **I** and **II** revealed a similar substitution pattern on the 1,4-dihydroquinolinone: N_1-alkylated, C_3-carboxylated, C_6-fluorinated, C_7−N-alkylated as well as C_8−O-alkylated.



I (Levofloxacin) **II** (Moxifloxacin)

The C_7−N bond of a fluoroquinolinone is normally constructed by the displacement of a 7-fluoro substituent with a primary or secondary amine; however, the reaction of an acid of general structure **1** directly with an amine often results in a low yield (<20%) of the C_7−N alkylated product **3** (Scheme 1, where R, R,[1] R^2, R^3 = H, acyclic, or cyclic substituents). In order to improve the yield of the desired compound **3** from this reaction, the C_7−F bond of acid **1** may be activated by the formation of a 4-(oxo-κO)-3-quinolinecarboxylato-κO3)-disubstituted boron complex (such as structure **2** shown in Scheme 1, where X = F, or OAc) before treating with an amine.[4–6] Recently, multi-hundred grams of difluoro−boron complex **5** was requested to support our ongoing drug research and development activities. Although the literature reported that complex **5** could be prepared in high yields (84−95%) by refluxing 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4**) in 48% tetrafluoroboric acid at 100 °C for 5−6 h,[4] this method was not a good choice for large-scale preparation of complex **5** due to the special equipment required to handle highly hazardous HBF_4.[7] Alternatively, the difluoro−boron complex **5** could be obtained in moderate to fair yields (50−78%) by refluxing acid **4** with a large excess (11.9 equiv) of boron−trifluoride etherate[8] in THF for 48−72 h;[5,9] however, a chromatographic purification was required to separate the desired complex **5** from unreacted acid **4** after workup on large scale. Herein, we report an improved nonchromatographic process for quantitative production of complex **5** with high chemical purity (≥99%).

Results and Discussion

An analysis of the reaction product profile of acid **4** and $BF_3 \cdot Et_2O$ in THF revealed that one mole of hydrogen fluoride, a highly corrosive acid,[9] was formed as a byproduct (Scheme 2). The moderate yield of difluoro−boron complex **5** might be

* Author for correspondence. Telephone: (908)707-3321. Fax: (908)526-6469. E-mail: xli6@prdus.jnj.com.

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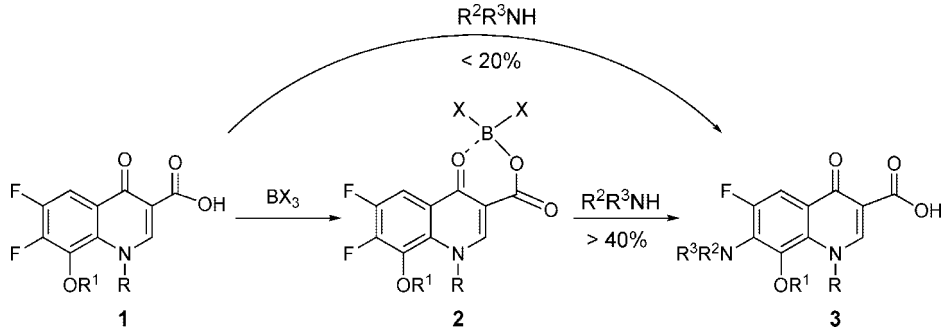
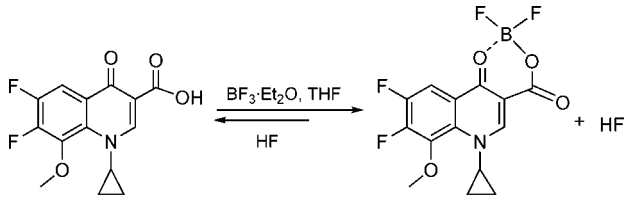
Scheme 1



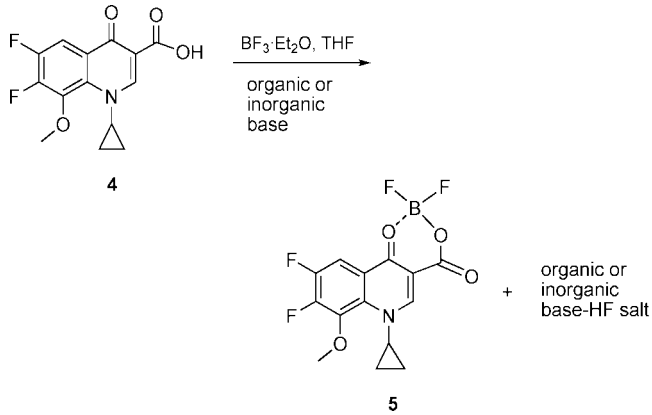
Scheme 2



attributed to the generation of HF from the reaction, which would cause a possible cleavage of complex **5** and shift the equilibrium back to acid **4**, leading to an incomplete reaction (entry 1, Table 1).[5]

A quick and simple solution to this problem was to add an organic or inorganic base (>1.0 equiv) to the reaction mixture to neutralize HF and drive the equilibrium toward to the desired product (Scheme 3). The first test of this theory was to add pyridine as the scavenger to produce a pyridine-HF salt in the reaction mixture.[10] In practice, acid **4** was treated with $BF_3 \cdot Et_2O$ (2.3 equiv) in the presence of pyridine (1.5 equiv) in refluxing THF for 3 h, to give a quantitative conversion of acid **4** to crude product that containing the desired complex **5** (86% chemical purity), plus 50% (wt %) of pyridinium hydrogen fluoride salt, as determined by ^{1}H NMR integration and HPLC analysis (entry 2). Column chromatography was used for purification because complex **5** could not be purified either by crystallization or by solvent partition. Similarly, triethylamine (1.35 equiv) was used to scavenge HF resulting in quantitative conversion of acid **4** to crude **5** with high chemical purity (98.6%); unfortunately, it was also difficult to isolate pure **5** from the triethylamine-HF salt (entry 3).

Scheme 3



In an effort to isolate difluoro−boron complex **5** without chromatography, we turned to the use of inorganic bases to scavenge HF as the solubilities of alkali-metal carbonates (such as Na_2CO_3 and K_2CO_3)[11] and fluorides (such as LiF, NaF, KF, RbF, and CsF)[12] have been reported to be very limited in organic solvents. For instance, both Na_2CO_3 and K_2CO_3 are insoluble in MeCN at 25 °C,[11] while the solubilities of NaF and KF are only 1.22 g/L and 1.78 g/L, respectively.[12] In contrast, the solubility of difluoro−boron complex **5** is fairly high (45.5 g/L) in CH_3CN at room temperature (20 °C),[13] which offered a possible nonchromatographic approach to purify **5** from an inorganic base-HF salt. Acid **4** was therefore treated with granular Na_2CO_3 (1.35 equiv) and $BF_3 \cdot Et_2O$ (1.35 equiv) in refluxing THF, but this heterogeneous reaction was incomplete after 8 h with a mixture of **4/5** (14.4%/82.0%, area %), as monitored by HPLC. When excess $BF_3 \cdot Et_2O$ (0.3 equiv) was added, the reaction went to completion within 10 h (total time) and afforded complex **5** with high chemical purity (98.3%), which however, was contaminated with some sodium salts (a mixture of NaF and/or $NaHCO_3$ and Na_2CO_3; 12%, wt %) (entry 4, Table 1) after purification of the crude product by slurry in MeCN.

On the other hand, when finely powdered K_2CO_3 (1.15 equiv, ~325 mesh) was used in the reaction with $BF_3 \cdot Et_2O$ (1.15 equiv) the reaction was complete in 6 h and afforded difluoro−boron complex **5** in nearly quantitative yield with high chemical purity (>99%) (entry 5, Table 1), using the same purification method (MeCN slurry) that was applied to the reaction with Na_2CO_3. The difluoro−boron complex **5** prepared by this process is almost salt free as analyzed by combustion elemental analysis (K < 40 ppm) and is stable for months without decomposition when stored at 20 °C under dark. The reaction with K_2CO_3 was reproducible and scaleable from small scale (2−50 g) to large scale (multihundred-gram to multikilogram). The complex **5** prepared by this method is an off-white crystalline solid, the structure of which was confirmed by a single crystal X-ray diffraction.[14]

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Table 1. **Results of the preparation of difluoro−boron complex 5 using organic and inorganic bases to scavenge HF**

entry	conditions	yield (%)[a]	purity (%)[b]
1	$BF_3 \cdot Et_2O$ (6.8 equiv), THF, 60 °C, 36 h	55−60	98.0[d]
2	$BF_3 \cdot Et_2O$ (2.3 equiv), pyridine (1.5 equiv), THF, 60 °C, 3 h	150[c]	86.0
3	$BF_3 \cdot Et_2O$ (1.8 equiv), Et_3N (1.35 equiv), THF, 60 °C, 3 h	149[c]	98.6
4	$BF_3 \cdot Et_2O$ (1.65 equiv), Na_2CO_3 (1.35 equiv), THF, 60 °C, 10 h	112[c]	98.3
5	$BF_3 \cdot Et_2O$ (1.35 equiv), K_2CO_3 (1.15 equiv), THF, 60 °C, 6 h	97.0	99.5[e]

[a] Isolated yield. [b] Determined by HPLC, area %. [c] Contaminated with organic/inorganic base-HF salt. [d] After chromatographic purification. [e] A result of multihundred gram runs.

Conclusions

After exploring various reaction conditions, a reproducible, nonchromatographic, and salt-free process was developed for large-scale production of difluoro−boron complex **5** in almost quantitative isolated yield with high chemical purity (>98%). The homogeneous reaction of acid **4** with $BF_3 \cdot Et_2O$ (1.8−2.3 equiv) and an organic base, such as pyridine or Et_3N (1.35−1.5 equiv), was complete within 3 h; however, the separation of the desired difluoro−boron complex **5** from the organic base-HF salt was problematic. On the other hand, Na_2CO_3 and K_2CO_3 (1.15−1.35 equiv) were demonstrated to be efficient scavengers of HF under the reaction conditions. K_2CO_3 was the inorganic base of choice since it reacted with HF to form an insoluble salt mixture of KF and/or $KHCO_3$ and K_2CO_3, which was easily separated from difluoro−boron complex **5** by filtration. This efficient process can be used for large-scale production of pure difluoro−boron complex **5** in standard glassware equipment.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. The melting point was uncorrected and determined on a Thomas-Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker Avance-400 instrument. Mass spectra were recorded on a Agilent Series 180 LC/MS instrument (positive/negative modes). The purity/impurity ratios were determined on a Agilent Series 1100 system, using a Phenomenex Luna C_{18} (2) column (4.6 mm ID × 50 mm, 5.0 micron) at 35 °C with flow rate of 1.0 mL/min and run time of 10.0 min. Solvents: A 80% H_2O + 0.05% TFA, B 20% CH_3CN; Gradient: B 20%/0.0 min, B 20%/1.0 min, B 90%/5.0 min, B 45%/8.0 min, B 20%/10.0 min.

(1-Cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-(oxo-κO)-3-quinoline-carboxylato-κO3)difluoro−Boron (5). A 12-L 4-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple, a condenser, a pressure-equalization dropping funnel, and a N_2 inlet adapter was charged with 1-cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**4**) (250.0 g, 0.847 mol), anhydrous THF (3.0 L), and K_2CO_3 (129.6 g, 0.938 mol, ∼325 mesh). This suspension was stirred at 20 °C under N_2 for 5 min, and $BF_3 \cdot Et_2O$ (123.4 mL, 0.938 mol) was added dropwise over a 5-min period (This was a gentle exothermic process; the reaction temperature elevated from 18 to 23 °C after the addition). After the addition, the mixture was heated to 66 °C and refluxed for 6 h. The progress of the reaction was monitored by HPLC and LC/MS, which showed ≥98.6% completion of the reaction at the end of the third hour and end of the fourth hour. (When the reaction was incomplete, for example, 10% of starting acid **4** was determined to be present in the reaction mixture, a little more $BF_3 \cdot Et_2O$ (20 mL, 0.158 mol) was added to the reaction, which drove the reaction to completion after refluxing an additional 2 h). The reaction was cooled to 20 °C and diluted with Et_2O (5.0 L) and stirred for 10 min (Et_2O was replaced by TBME when production was on multikilogram scale). The solid was filtered and washed with Et_2O (100 mL × 2) and then dried at 50 °C under house vacuum (∼160 mmHg) for 20 h to afford 398.0 g (137% isolated yield, HPLC = 98.4%, area %) of crude difluoro−boron complex **5**. This crude solid was suspended in MeCN (4.0 L) and stirred at 20 °C for 20 min, and the solid was filtered and washed with MeCN (100 mL). The filtration cake was resuspended and stirred in MeCN three more times (2.0 L × 3, or until no more **5** could be detected by HPLC in the filtrate), and all filtrates were combined and concentrated at 60 °C under high vacuum (∼20 mmHg). The resulting off-white crystalline solid was dried at 50 °C under house vacuum (∼160 mmHg) for 20 h to afford 282.6 g (97% isolated yield, HPLC = 99.6%, area %) of pure difluoro−boron complex **5**. HPLC (area %/retention time): **4**, <0.5%/4.64 min; and **5**, 99.5%/4.39 min. Mp = 226−228 °C. ^{1}H NMR (400 MHz, CD_3CN) δ 1.22 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2), 4.16 (s, 3 H, OCH_3), 4.48 (m, 1 H, CH), 8.18 (dd, J = 9.6, 8.0, 1 H, H_5), 9.16 (s, 1 H, H_2). LC-MS m/z 344 (MH^+), 709 ([2M + Na]$^+$). Calcd for $C_{14}H_{10}BF_4NO_4$: C, 49.02; H, 2.94; N, 4.08; B, 3.15; F, 22.15. Found: C, 49.18; H, 2.86; N, 3.91; B, 3.36; F, 22.03.

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