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A High-Throughput Impurity-Free Process for Gatifloxacin

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Abstract:

An improved process to obtain gatifloxacin (1) through use of boron chelate intermediates has been developed. The methodology involves an initial activation step which accelerates the formation of the first chelate under low-temperature conditions and prevents demethylation of the starting material. To increase the overall yield and to avoid the isolation and manipulation of the resulting intermediates, the process has been designed to be carried out in one pot. As a result, we present here an easy, scaleable and substantially impurity-free process to obtain gatifloxacin (1) in high yield.

1. Introduction

Gatifloxacin is the common name for (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (**1**), one of the most important broad-spectrum antibacterial agents and a member of the fourth-generation fluoroquinolone family.[1] Fluoroquinolones inhibit the enzyme DNA gyrase (topoisomerase II), which is responsible for the supercoiling of the DNA double helix, preventing the replication and repair of bacterial DNA and RNA.[2] Gatifloxacin (**1**) reached the market in 1999 under the brand name Tequin for the treatment of respiratory tract infections. The drug is available as tablets and aqueous solutions for intravenous therapy as well as eye drop formulation (Zymar).

To date, there are several processes described for the preparation of gatifloxacin, which can be grouped into two main categories: direct substitution of the 7-position fluorine atom of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (**2**) by 2-methylpiperazine (Scheme 1),[3−5] and through boron chelate-type intermediates to overcome the diminished reactivity induced by the 8-methoxy group, which uses as starting material the ethyl ester derivative **3** (Scheme 2).[6−9]

In the first approach, very different results have been reported carrying out similar procedures. First, the reaction of **2** with 2-methylpiperazine for 2 h at 70−95 °C in dimethylsulfoxide was reported to proceed with low yield (20%).[3] More recently, a good yield (84%) has been reported for the same transformation when the reaction is performed at 55 °C for 24 h.[4] However, we have repeated this procedure several times, obtaining only moderate yields (58%) in the crude gatifloxacin isolation and 13.6% of byproduct **4** formed during the reaction. Taking into account that no purification yields were given in the latter work, our results are more in agreement with those reported in the former procedure.

We have found that this route gives rise to large quantities of nondesired 1-cyclopropyl-6,7-difluor-1,4-dihydro-8-hydroxy-4-oxo-3-quinoline carboxylic acid (**4**, Scheme 1), resulting from demethylation of **2**, which seems to be the main cause of the low reaction yield. Our studies have demonstrated that demethylation takes place not only in dimethylsulfoxide but also in other polar aprotic solvents such as dimethylacetamide, *N*-methyl-2-pyrrolidone or acetonitrile and in the presence of either organic or inorganic bases. In addition, this process also involves laborious workup that makes it difficult to scale up, because it requires distillation of large amounts of dimethylsulfoxide or column chromatography purifications.

To improve the overall yield of the process using this route, a new procedure, in which a regeneration step from compound **4** is included, has been recently reported.[5] The authors considered that the demethylation of compound **2** is due to the hydrogen fluoride formed in the reaction, and also mentioned the slow precipitation of the crude gatifloxacin from the reaction mixture as jointly responsible for the low yield. Thus, to increase the yield the precipitation was carried out over 24 h at a pH value between 10.1 and 10.7 in a temperature range of 20−35 °C. Further treatment of the filtrate with methylating agents led to the starting carboxylic acid **2**, which is subsequently treated with 2-methylpiperazine to improve the total yield. Overall, 52.0−54.7% yields were reported for the crude gatifloxacin isolation. The yield after two recrystallization steps was between 38.2−44.8% and 17% of starting acid **2** was recovered after treatment with dimethyl sulfate.

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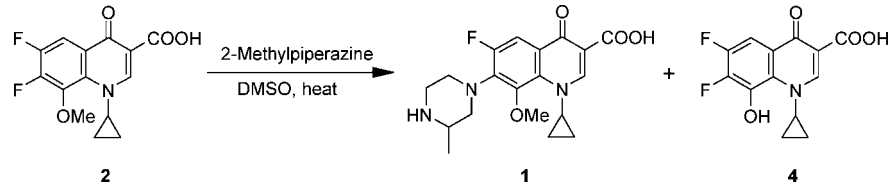
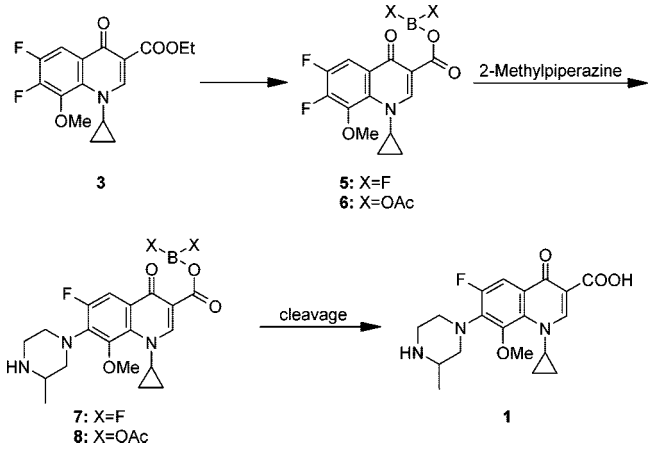
Scheme 1. **Direct coupling to obtain gatifloxacin (1)**



2 1 4

Scheme 2. **Synthesis of gatifloxacin (1) through boron chelate-type intermediates**



3 **5:** X=F **6:** X=OAc **7:** X=F **8:** X=OAc 1

On the other hand, by following the second strategy, employing boron chelates, yields from low (39−44%)[6−8] to moderate (72%)[9] have been reported, depending on the nature of the species involved, either the boron difluoride chelates **5** and **7** or the boron diacetoxy chelates **6** and **8**, respectively (Scheme 2). However, by using this approach the demethylation of the starting material is only partially avoided, and the isolation of the intermediates **5** and **7** or **6** and **8** results in the loss of yield in mother liquors and the manipulation of toxic intermediates.[10] In the case of the boron difluoride chelates, the procedure has also been carried out without isolation of **7**;[7,8] however, the yield of the process was not significantly improved. In the second case, using diacetoxy chelates, the synthesis of **6** proceeds with the formation of enormous quantities of acetic acid, which prevents the adaptation of the procedure to a one-pot process.

2. Results and Discussion

In order to obtain gatifloxacin easily and with higher yield, we have designed a new process in which some modifications have been carried out over the second general approach that uses boron difluoride chelates.

2.1. Redesign of the Manufacture Process for 5. Our studies in the laboratory revealed that most of the demethylation of the starting materials in both processes takes place due to the increasing concentration of alkylammonium salts in the reaction medium, although it may not be the only reason.[11,12] However, when **2** was treated with boron trifluoride-diethyl etherate in the absence of any base, no demethylation was detected, but the reaction needed high quantities of boron trifluoride to reach completion. On the other hand, when an organic base such as triethylamine, diisopropylethylamine, or 2-methylpiperazine itself was employed, quantities of around 10% of **4** were detected in the most favourable case. Demethylation of **2** has also been observed when an inorganic base such as sodium bicarbonate was used.

Since the utilization of a base becomes necessary to trap the hydrogen fluoride formed during the reaction progress, we designed a new procedure in which the use of a base became unnecessary. Thus, the carboxylic acid **2** was readily converted into the trimethylsilyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (**9**) by treatment with 1,1,1,3,3,3-hexamethyldisilazane in refluxing acetonitrile for 1 h (Scheme 3).[13,14] This intermediate not only allowed us to carry out the reaction with boron trifluoride-diethyl etherate in the absence of base, but also resulted in the rapid formation of **5** and at low temperatures due to the increased reactivity of the carboxylate moiety when compared with that from **2**. Fluorotrimethylsilane[15] was formed as byproduct, and no significant amounts of nondesired compound **4** were detected.

2.2. Redesign of the Manufacture Process for 1. Once demethylation of the starting carboxylic acid **2** was overcome, the overall yield of the process was further improved, adapting it to a one-pot process. Thus, not only was the total yield increased, but the manipulation of toxic boron chelate-type intermediates was also conveniently avoided.

After the formation of **5** was completed, the pH of the reaction mixture was taken to 8.5−9.5 with triethylamine prior to the 2-methylpiperazine addition to avoid additional waste of the latter trapping the hydrogen fluoride, which evolves during the reaction. Thus, the coupling between chelate **5** and 2-methylpiperazine takes place between 15−25 °C, which is important because **5** can be converted to the carboxylic acid **2** by heating, which would be demethylated in the presence of

(10) These compounds are known to be irritants and produce a nasty taste in the mouth.

(11) We have observed that treating **2** with triethylamine (2.5 equiv) in 1 volume of dimethylacetamide (100 °C, 2 h) or acetonitrile (reflux, 2 h), 41% and 37% of **4** were formed, respectively. In addition, when diisopropylethylamine was employed instead of triethylamine, under the same conditions, 4.7% and 5.8% of **4** were formed, respectively.

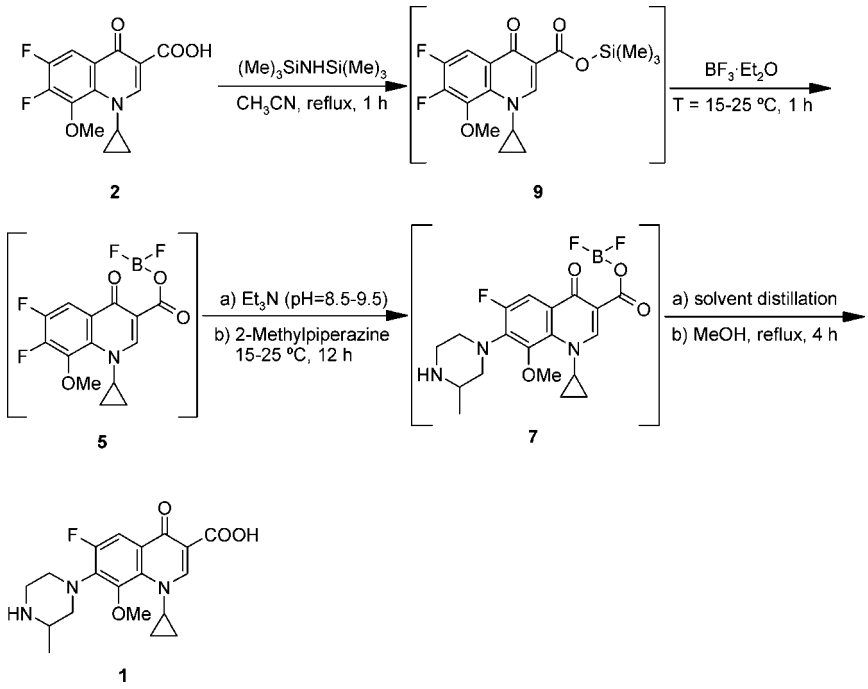
(12) A method for the selective cleavage of primary alkyl aryl ethers with boron trichloride/tetra-*n*-butylammonium iodide, which uses slightly similar conditions to those used in the synthesis of gatifloxacin through boron chelates, has been reported by Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719.

(13) Although the formation of trimethylsilyl ester **9** is probably immediate, reflux is kept for 1 h in order to ensure elimination of all ammonia gas.

(14) Palomo, F. E.; Solis, O.; Palomo, A. L. Trimethylsilyl esters and solvates of chelates of quinoline-3-carboxylic acids, and their preparation and use in a process for quinolone antibacterialsES 2 077 490 A1, 1995.

(15) Fluorotrimethylsilane (bp: 16 °C) is converted into the less volatile methoxytrimethylsilane (bp: 57−58 °C) in the subsequent distillation, in which the condensed solvent vapors are treated with a solution of sodium methoxide in methanol. To ensure the complete conversion of all formed fluorotrimethylsilane, solvents and gases that might pass through the pump are bubbled into the same solution. The resulting solution of methoxytrimethylsilane is treated as organic waste.

Scheme 3. **One-pot process to obtain gatifloxacin (1)**



the triethylammonium or 2-methylpiperazonium salts that are formed during the coupling. This aspect is also important because the temperature becomes critical in this step, and therefore, it should be maintained below 35 °C to avoid chelate **5** cleavage and the subsequent demethylation.

The previously described final cleavage step to obtain gatifloxacin (**1**) involved refluxing **7** in a mixture of ethanol/triethylamine (10:1; v/v)[7] or in aqueous ethanol (80%) with[6] or without[8] the presence of triethylamine. However, we found refluxing **7** in methanol during 3−4 h to be sufficient to perform this cleavage without the need of base or water. Furthermore, we have discovered that the subsequent crystallization to obtain crude gatifloxacin (**1**) gives rise to good crystals that allow the isolation from the reaction mixture faster than in other solvents and shortening significantly the filtration times at large scale. Thus, the use of water and/or triethylamine is avoided and the loss of yield in mother liquors minimized.

As a result, gatifloxacin (**1**) is prepared with very good yields (above 96% in formed gatifloxacin and 91% in the isolation) and purity above 99.7% by HPLC with only one impurity in a level higher than 0.1%. Nevertheless, if required, higher purity can be achieved by further recrystallization from methanol/water (9:1, v/v) to obtain more than 99.85% of purity with an overall yield of 85%.[16] This coupling process has been successfully tested with other amines such as piperazine and *N*-methylpiperazine with yields above 95% in the formation for both compounds, and 79% and 90% yield, respectively, in isolated product. Furthermore, this process is currently being adapted for the manufacture of moxifloxacin, another important broad-spectrum antibacterial agent, for which yields above 95% in formed product have already been obtained. Similarly, the procedure described herein could find further applications in the synthesis of other known fluoroquinolones with different quinolonic scaffolds, such as ciprofloxacin or levofloxacin.

(16) Yields were calculated as the average of three batches. Yields for individual batches were: batch 1, 32.3 kg, 85%; batch 2, 33.2 kg, 87%; batch 3, 31.8 kg, 83%.

3. Conclusion

An improved method for the manufacture of gatifloxacin (**1**) from 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (**2**) has been developed. In this process the distillation of large quantities of dimethylsulfoxide, which make it difficult to scale up, has been avoided and the yield has been notably improved by avoiding the formation of nondesired compound **4** resulting from demethylation of the starting material. In addition, the whole process has been performed in one-pot, avoiding isolation and manipulation of the toxic intermediates **5** and **7** and minimizing loss of yield in mother liquors. Considerably higher yields than those previously reported were obtained with a high purity without the need of further purification, although purity can be further improved by recrystallization if desired. The process has also been successfully scaled up to 30-kg batches without significant variations in yield, reaction times, or purity.

4. Experimental Section

HPLC chromatography was performed using a Waters 2487 HPLC instrument. Reactions were monitored under the following conditions: Step 2, Inertsil ODS-3V, 5 μm, 250 mm × 4.6 mm column at 30 °C with monitoring at 235 nm. Flow rate 1.5 mL/min, mobile phase buffer/CH_3CN (50:50). Buffer preparation, 5 mL of triethylamine in 950 mL of H_2O adjusted to pH 3 with H_3PO_4 (85%). Analysis time 15 min, injection 20 μL. Step 3, the same conditions as above but monitoring at 225 nm. Step 4, Prodigy C8, 5 μm, 250 mm × 4.6 mm column at 30 °C with monitoring at 278 nm. Flow rate 1.0 mL/min, mobile phase buffer/CH_3OH (60:40). Buffer preparation, 7.8 g of $NaH_2PO_4 \cdot H_2O$ and 4.7 g of 1-hexane sulfonic acid sodium salt monohydrate in 950 mL of H_2O adjusted to pH 2.4 with

H_3PO_4 (85%). Analysis time 15 min, injection 20 μL. The same conditions for step 4 were employed for the purity and assay HPLC analysis, but the analysis time was changed to 60 min in the purity HPLC analysis. Melting points were determined in open capillaries on a Buchi melting point B-545 apparatus and are uncorrected.

4.1. (±)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic Acid (1), One-Pot Process Conditions. *Step 1. Preparation of Trimethylsilyl Ester 9.* A suitable reactor was charged with 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (**2**) (30 kg, 101.6 mol) and acetonitrile (70 kg) under nitrogen atmosphere. The mixture was heated to reflux (75−80 °C), and 1,1,1,3,3,3-hexamethyldisilazane (9.9 kg, 61.3 mol) was added, keeping the temperature above 70 °C but avoiding ammonia release becoming too vigorous. The mixture was maintained under reflux during 1 h and then cooled to $T = 0-15$ °C. A crude sample of **9** was obtained by filtration under nitrogen stream. However, in $CDCl_3$ solution a 2:1 relation between trimethylsilyl ester **9**/carboxylic acid **2** was observed when a rapid analysis was carried out. This is due to the high instability of **9** out of the reaction conditions that makes it almost impossible to perform the ^{13}C NMR analysis. In the same way, elemental analysis data are slightly out of the ±0.4 deviation range (C, +0.47; H, −0.41; N, +0.47). MS *m/z* 367 (M^+); ^1H NMR ($CDCl_3$) δ 1.02 (m, 2H), 1.18 (m, 2H), 3.95 (m, 1H), 4.05 (d, $J_{H-F} = 2.1$ Hz, 3H), 7.97 (dd, $J_{H-F} = 10.4$ Hz, $J_{H-F} = 8.8$ Hz, 1H), 8.57 (s, 1H). Anal. Calcd for $C_{17}H_{19}NO_4F_2Si$; C, 55.57; H, 5.21; N, 3.81. Found: C, 56.04; H, 4.80; N, 4.28.

Step 2. Chelation. To the resulting suspension was added boron trifluoride-diethyl etherate (17.4 kg, 122.6 mol), keeping the temperature between 0−15 °C, and the mixture was stirred under these conditions for 1 h.

Step 3. Coupling. The pH of the mixture was then adjusted to 8.5−9.5 with triethylamine[17] (10.3 kg), keeping the temperature below 25 °C, and then a solution of 2-methylpiperazine (30.6 kg, 305.5 mol) in acetonitrile (66 kg) was added at $T =$ 15−25 °C. The resulting mixture was stirred at $T = 15-25$ °C for 12 h, and then solvents were removed under reduced pressure to obtain a stirrable slurry.

Step 4. Cleavage. Methanol (118 kg) was added, and the resulting yellow suspension was heated to reflux (60−65 °C) for 4 h. The mixture was then cooled to 15−25 °C and stirred at that temperature until a generous precipitate was formed. The resulting white suspension was then cooled at $T = 0-5$ °C and kept at that temperature for an additional hour. The cool suspension was filtered, washed with methanol (47 kg), and dried at 30−40 °C under vacuum to obtain crude gatifloxacin (**1**) as slightly yellowish white crystals. Yield 34.7 kg, (91%); purity by HPLC 99.76%.

Step 5 (If required). Purification. Wet gatifloxacin (wet weight 52.8 kg; estimated dry weight 34.7 kg), methanol (750 kg), and water (84 kg) were mixed in a suitable reactor filled with nitrogen. The resulting suspension was heated to reflux (65−70 °C) to obtain a clear solution and then cooled to 15−25 °C until an abundant suspension was obtained. The mixture was then cooled between −5 to 5 °C for an additional hour and then filtered, washed with a mixture of methanol (50.7 kg) and water (5.6 kg), and dried at 30−40 °C under vacuum to obtain pure gatifloxacin (**1**) as white crystals. Yield 32.3 kg, (93%); purity by HPLC 99.87%; Assay by HPLC 100.8%; mp 167−168 °C[18] (Lit. [7] 159−162 °C). Water content by Karl Fischer 3.0%[19] MS *m/z* 376 ($M^+ + H$); ^1H NMR (DMSO-d_6) δ 0.97 (d, $J = 6.1$ Hz, 3H), 1.04 (m, 2H), 1.15 (m, 2H), 2.75−2.94 (m, 4H) 3.14 (m, 1H), 3.30 (m, 2H), 3.74 (s, 3H), 4.15 (m, 1H), 7.70 (d, $J_{H-F} = 12.2$ Hz, 1H), 8.67 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 8.40, 8.42, 18.66, 40.28, 45.46, 50.17, 50.29 (d, $J_{C-F} = 3.44$ Hz), 57.36 (d, $J_{C-F} = 3.74$ Hz), 62.15, 106.0 (d, $J_{C-F} = 22.7$ Hz), 106.04, 120.05 (d, $J_{C-F} = 8.6$ Hz), 133.6 (d, $J_{C-F} = 1.1$ Hz), 138.9 (d, $J_{C-F} = 11.9$ Hz), 145.2 (d, $J_{C-F} = 5.87$ Hz), 149.88, 155.06 (d, $J_{C-F} = 249.2$ Hz), 165.56, 175.56 (d, $J_{C-F} = 3.3$ Hz). ^{19}F NMR (DMSO-d_6) δ −120.4 (d, $J = 12.2$ Hz). Anal. Calcd for $C_{19}H_{22}N_3O_4F + 3.0\%$ H_2O; C, 58.95; H, 6.07; N, 10.85. Found: C, 58.90; H, 5.82; N, 10.90. Boron content 170 ppm.[20]

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Supporting Information Available

DSC and TGA graphics of compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Samples were diluted in water (1:1; v/v) to carry out the pH measurements.

(18) DSC analysis showed two endothermic peaks at 166.2 °C (*T* onset = 164.3 °C) and 190.0 °C (*T* onset = 188.2 °C) and an exothermic one at 168.1 °C. The shape of this DSC curve is characteristic of a monotropic transition between crystalline forms.

(19) Although there are several hydrates described for gatifloxacin such as, among others, the hemimydrate, sesquihydrate, and pentahydrate (Raghavan, K. S.; Ranadive, S. A.; Gougoutas, J. Z.; Dimarco, J. D.; Parker, W. L.; Dovich, M.; Neuman, A. Gatifloxacin pentahydrate. WO 2002/22126 A1, 2002), the Gatifloxacin obtained by the present procedure does not seem to form a stoichometric hydrate, but instead it retains moisture. Thus, the product is usually obtained with a Karl-Fischer value below 1% after drying, but it can absorb moisture until a final content of about 3%. This water content can vary between 2.0% and 3.5%, depending on the relative humidity of the environment. DSC analysis revealed a broad endothermic signal with minimum at 76 °C, while TGA analysis showed that the product loses all the water below 80 °C. No loss of weight is registered when the product melts, and the weight is constant until the decomposition of the material at about 200 °C. On the basis of these results, it can be said that the water content of the gatifloxacin obtained by the present process is retained moisture instead of water belonging to the lattice. The shape of the derivative of the weight curve at the beginning of the analysis shows that the sample has already lost part of the moisture when the register starts. This is probably due to the sample starting to lose weight when makes contact with the dry atmosphere of the TGA oven that could explain the different values obtained for water content of the analyzed sample by TGA (1.90%) and Karl-Fischer (2.64%) methods.

(20) The respective boron contents found for batches 2 and 3 were 160 and 300 ppm.