Chlorination at the 8-Position of a Functionalized Quinolone and the Synthesis of Quinolone Antibiotic ABT-492

David M. Barnes,* Alan C. Christesen, Kenneth M. Engstrom, Anthony R. Haight, Margaret C. Hsu, Elaine C. Lee, Matthew J. Peterson, Daniel J. Plata, Prasad S. Raje, Eric J. Stoner, Jason S. Tedrow, and Seble Wagaw

GPRD Process Research and Development, Abbott Laboratories, Bldg. R8/1, 1401 Sheridan Road, North Chicago, Illinois 60064-6285, U.S.A.

Abstract:

The total synthesis of quinolone antibiotic ABT-492 has been achieved in 67% yield over nine steps from 2,4,5-trifluorobenzoic acid. The highlights of this synthesis include a novel chemoselective chlorination at the 8-position of a highly elaborated quinolone core. In addition, a Lewis acid promoted cyclization reaction to form the quinolone heterocycle was developed which was incorporated into a one-pot, three-step cyclization/coupling/protection sequence that proceeds in 93% yield.

Introduction

First introduced in the 1970s, the fluoroquinolone class of antibiotics has assumed an expanding role in the treatment of bacterial infections.¹ Due to the increasing incidence of bacterial resistance to specific antibiotic chemotherapies, research continues into the discovery and development of new and more potent quinolone antibiotics.¹ Quinolones halogenated at the 8-position are often particularly potent.² ABT-492, an 8-chloro-6-fluoro-quinolone derivative, has been shown to possess good in vitro activity against Grampositive and Gram-negative strains and has been selected for clinical development.³

A retrosynthetic analysis of ABT-492 is shown in Scheme 1 and is typical for this class of molecule.⁴ The starting material for this retrosynthesis would be 3-chloro-2,4,5-trifluorobenzoic acid (**1a**, X = Cl);⁵ however this approach suffered from uncertain supplies and long lead times for the acquisition of **1a**. Therefore, we investigated alternative, nonchlorinated starting materials. In this paper, we describe our synthesis of ABT-492 from 2,4,5-trifluorobenzoic acid (**1b**, X = H), which was enabled by our development of a late-stage, mild chlorination of the 8-position. Our first generation process employed 1,3-dichloro-5,5,-dimethylhy-

* To whom correspondence should be addressed. E-mail: david.barnes@abbott.com.

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- (3) Harnett, S. J.; Fraise, A. P.; Andrews, J. M.; Jevons, G.; Brenwald, N. P.; Wise, R. Journal of Antimicrobial Chemotherapy 2004, 53, 783–792.
- (4) Da Silva, A. D.; De Almeida, M. V.; De Souza, M. V. N.; Couri, M. R. C. Current Medicinal Chemistry 2003, 10, 21–39.
- (5) For example, see: Mealy, N. E.; Castaner, J. *Drugs of the Future* 2002, 27, 1033–1038 in which the synthesis of ABT-492 from ethyl 3-chloro-2,4,5-trifluorobenzoyl acetate is described.

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Scheme 1. Retrosynthesis of ABT-492



dantoin (DCH) as an electrophilic chlorine source.⁶ This mild, selective chlorination reagent is readily available and safe, and its byproducts are nontoxic. Later we determined that the use of NCS, catalyzed by protic acids, afforded excellent yields without the use of halogenated solvents.

Results and Discussion

We initially investigated the chlorination of acetate **2a** (eq 1). According to a previous report, a 6-fluoro-7-



aminoquinolone derivative was chlorinated at the 8-position using SO_2Cl_2 in chloroform.⁷ When acetate **2a** was treated under these conditions, chloroacetate **3** was indeed formed but opening of the azetidine ring to form chloride **4** (>1%) proved to be an unavoidable side reaction; this impurity was difficult to separate from the desired product **3**. The formation

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⁽⁶⁾ Orazi, O. O.; Salellas, J. F.; Fondovila, M. E.; Corral, R. A.; Mercere, N. M. I.; de Alvares, E. C. R. Anales Asoc. Quim. Arg. 1952, 40, 61–73.

⁽⁷⁾ Araki, K.; Kuroda, T.; Uemori, S.; Moriguchi, A.; Ikeda, Y. J. Med. Chem. 1993, 36, 1356–1363.

Scheme 2. Effect of ester protecting group on solubility



of **4** was attributed to the harshly acidic conditions accompanying the use of SO_2Cl_2 ; therefore milder conditions were explored.⁸ It was found that DCH in CH₂Cl₂ cleanly chlorinated the quinolone ring at the 8-position, and chloroacetate **3** was obtained with high purity in 87% isolated yield. Although DCH is commonly employed as an inexpensive chlorine source for water treatment,⁹ its use in aromatic chlorination has been surprisingly rare.^{6,10}

1 mol equiv of the hydantoin is employed in this reaction. While the second chlorine on the hydantoin has been demonstrated to be capable of chlorinating the quinolone ring, the slower rate of the second chlorine transfer results in the generation of additional byproducts over the extended reaction time. With 1 mol equiv of DCH, the excess chlorine oxidant can be cleanly decomposed with NaHSO₃ at the end of the reaction.

This procedure completely consumes the starting material and provides the chlorinated quinolone in good overall yield in CH₂Cl₂. We have found that while the reaction proceeds in EtOAc or MeCN, consumption of the starting material was inconsistent. For example, in EtOAc, 2-5% of the starting material typically remains even after stirring overnight, and little of this intermediate is rejected in later isolations.

These conversion issues were subsequently determined to be the result of the low solubilities of both the starting material and product of the reaction. When the reaction was sampled after stalling, it was found that no starting material remained in solution though starting material was detected in the solids. Apparently, as chloroacetate **3** crystallizes during the course of the reaction, acetate **2a** is entrained in the solid.

An increase in the solubilities of the reaction components would be expected to alleviate the entrainment problems. To modulate the solubility of the chlorination substrate and product, we prepared alternative ester-protected substrates and measured their solubilities in EtOAc. From this screen, it was found that the isobutyrate ester provided a significant solubility enhancement relative to the other groups examined (**2b**, **2d**, Scheme 2). Indeed, the propionate and benzoate esters did display incomplete conversion when subjected to chlorination reactions employing DCH in EtOAc.

(9) Rao, Z.; Zhang, X.; Baeyens, W. R. G. *Talanta*, 2002, *57*, 993–998.
(10) For the chlorination of *N*,*N*-dimethylaniline using DCH, see: Chao, T. H.; Cipriani, L. P. *J. Org. Chem.* 1961, *26*, 1079–1081. For the use of DCH in the chlorination of aryl boronic acids, see: Szumigala, R. H., Jr.; Devine, P. N.; Gauthier, D. R., Jr.; Volante, R. P. *J. Org. Chem.* 2004, *69*, 566– 569. Our synthesis of isobutyrate ester 2c is described in Scheme 3. Starting from 2,3,5-trifluorobenzoic acid, acid chloride formation is followed by reaction with the reagent derived from potassium ethyl malonate and MgCl₂,¹¹ affording ketoester **5** which is isolated in 94% yield (two steps). Condensation of ketoester **5** with triethylorthoformate provides a vinylagous ester, which in turn is condensed with 2,6-diamino-3,5-difluoropyridine (**6**) in MeCN/NMP to prepare vinylagous amide **7** in 93% isolated yield and with >95% purity.

Our initial cyclization conditions to isolate quinolone core **8** employed K_2CO_3 in DMSO at 60 °C, but this resulted in significant disproportionation to a mixture of bis-quinolones **9** (eq 2, hydroxyl-substituted **9b** results from attack of water on **9a**). We postulate that under these basic conditions,



diaminopyridine 6 was an acceptable leaving group so that amide exchange could occur with core 8. We later found that when the reaction was promoted by a Lewis acid, no disproportionation was observed. This is likely due to the fact that deprotonation became rapid, thus removing the protonated (and electrophilic) starting material from the reaction medium.

Formation of isobutyrate ester 2c was ultimately accomplished via a three-step, one-pot procedure. First, cyclization was induced by DBU in the presence of 2 equiv of LiCl. Because of the activating effect of the lithium ion, this reaction proceeds at ambient temperature and without disproportionation. To the resulting solution was added 3-azetidinol hydrochloride and additional DBU, to effect the coupling reaction. While less than 2 equiv of LiCl were required to promote the cyclization, the additional LiCl accelerated the amine coupling, leading to cleaner reactions at lower temperatures. Also, while Et₃N is a sufficiently strong base for the cyclization reaction, it was found that DBU was more effective in deprotonating the azetidine. When the coupling reaction was run using inorganic base (KHCO₃, 60 °C), 1% of bis-coupled product 10 was observed at 99% conversion. Under the LiCl-promoted conditions, the reaction can be pushed to 99.5% conversion with similar levels of byproduct 10.



Finally, isobutyric anhydride was added to acylate the alcohol. The product was crystallized by the addition of

⁽⁸⁾ Buffering the reaction with NaOAc helped (0.5 to 1% ring-opening observed) but did not completely alleviate the problem.

Scheme 3. Preparation of isobutyrate ester 2c



aqueous citric acid; isobutyrate ester 2c was obtained in 93% yield from vinylagous amide 7 employing this sequence. Other Lewis acids (MgCl₂ and ZnCl₂) were screened in this sequence; MgCl₂ proved effective in promoting the cyclization reaction, but the three-step one-pot reactions were less clean.

As an interesting side note, we also found that the cyclization reaction could be made catalytic in metal (eq 3). Substoichiometric (20 mol %) use of MgCl₂ was ineffective (presumably due to fluoride ion poisoning of the Lewis acid). However, addition of TMSCl as a fluoride scavenger proved effective, and complete conversion was observed in about 3 h.



The chlorination of isobutyrate ester 2c using DCH in CH₂Cl₂ worked well (eq 4), providing the chlorinated quinolone 11 in 91% yield as its MTBE solvate. When we investigated alternative solvents, chlorination in EtOAc now resulted in complete conversion as desired. However, we observed variable isolated yields (<85%), presumably due to overchlorination during extended reaction times (a large number of small byproducts were observed by HPLC).



(11) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. Synthesis 1993, 290– 292. The reported procedure employs an aging of the reagent mixture for 6 h at 35 °C.

Table 1. Effect of acids on chlorinations using NCS



We therefore concluded that a less electrophilic chlorinating agent was required. *N*-Chlorosuccinimide showed promise when catalyzed by acids in EtOAc.¹² Screening of acids showed several conditions to be effective; in particular, reactions employing HClO₄, H₂SO₄, and H₃PO₄ proceeded in high yield and purity (Table 1, eq 5).

Aqueous HClO₄ gave superior yield, purity, and product color. In addition, it was felt that the use of an aqueous acid source would circumvent the safety concerns associated with anhydrous perchloric acid. However, when reaction mixtures were monitored by KF coulometry, we observed that the water content fell due to the acid-catalyzed hydrolysis of EtOAc. Therefore, H_3PO_4 and H_2SO_4 were chosen for additional investigation. Our final conditions employed 6.5 mol % H_2SO_4 in 9:1 EtOAc/MeOAc,¹³ and the product was obtained in 91% yield and 99% purity. Following a solvent switch to 2-propanol and subsequent saponification, ABT-

⁽¹²⁾ Goldberg, Y.; Alper, H. J. Org. Chem. 1993, 58, 3072. In the absence of added acid, no reaction was observed.

⁽¹³⁾ This solvent combination afforded the cleanest product, presumably due to the slightly higher solubilities afforded by the MeOAc cosolvent.

492 was isolated in 88–91% yield for the two steps (eq 6). Thus, the synthesis of ABT-492 was accomplished in 70% overall yield over nine transformations from trifluorobenzoic acid.



The mechanism of the acid-catalyzed NCS chlorination reaction is unclear. It has been proposed that treatment of NCS with $HCIO_4$ in hexanes, where the NCS is insoluble, generates $Cl^+ CIO_4^-$ as the reactive chlorinating species.¹² However, it also seems reasonable that, under the current conditions, where NCS is soluble, the active oxidant could be a protonated form of NCS.¹⁴

In conclusion, we have developed new chlorination reaction conditions for the installation of chlorine at the 8-position of a quinolone substrate, which were employed in the synthesis of the quinolone antibiotic ABT-492. These conditions are notable for their mildness, which permitted their use in the presence of an acid-sensitive azetidine moiety.

Experimental Section

Ethyl 2,4,5-trifluorobenzoyl acetate (5).¹⁵¹⁵ A reactor is charged with 2,4,5-trifluorobenzoic acid (1a, 139.5 kg, 792 mol), toluene (613 kg), and DMF (8.4 kg, 14 mol %), followed by thionyl chloride (139.4 kg, 1.58 equiv). The contents are brought up to 60 ± 5 °C and mixed until the starting acid is consumed (typically 3 h). (Caution: A large amount of outgassing is observed in this process.) After cooling the contents to 25 °C, the solution is distilled under vacuum until approximately 750 L are left. Fresh toluene (600 kg) is added, and a second distillation was brought down to 750 L. The final acid chloride solution is then used without further purification.

Potassium ethyl malonate (50.8 kg, 298 mol), magnesium chloride (34.5 kg, 362 mol), and toluene (130 kg) are cooled to ~0 °C, and THF (265 kg) is added while keeping the temperature <10 °C. The slurry is cooled again to 0 °C, and triethylamine (75 kg, 742 mol) is charged. The suspension is warmed to 50 °C and held for 1 h at which point the solution becomes visibly thinner. The free flowing suspension is recooled to 0 °C and stirred for 1 h. The acid chloride toluene solution (163 Kg) precooled to 0 °C is charged to the enolate over 50 min while keeping it <10 °C (the reactor jacket was set at -10 °C). Typically the reaction is complete within 10 min.

The yellow suspension is slowly added to hydrochloric acid (309 kg of water and 98 kg of concentrated HCl),

keeping the temperature <20 °C. After separating layers, the organic layer is washed with water (83 kg).

After a second run, the organic layers are combined and distilled under a vacuum, and ethanol is added twice as a chase distillation. The slurry was heated to \sim 45 °C until all the solids dissolve. The solution is cooled to 0 °C, and water (112 kg) is added to the resulting slurry. Following filtration, the wetcake is washed with a cold 50% aqueous ethanol solution and dried under a vacuum to give 85.6 kg of ethyl (2,4,5-trifluorobenzoyl)acetate **5** as a white solid (94% yield from 2,4,5-trifluorobenzoic acid).

¹H NMR (CDCl₃) (**keto**) δ 7.75 (ddd, J = 10.8, 10.8, 6.0 Hz, 1H), 7.02 (ddd, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.95 (d, 4.2 Hz, 2H), 1.35 (t, J = 7.3 Hz, 3H); (**enol**) δ 12.72 (s, 1H), 7.85 (ddd, J = 10.5, 9.6, 6.6 Hz, 1H), 6.96 (ddd, J = 10.5, 10.5, 6.6 Hz, 1H), 5.84 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H).

3-(2,4,5-Trifluorophenyl)-2-(*N*-[6'-amino-3',5'-difluoro]aminopyridine)methylene-3-oxopropionic Acid, Ethyl Ester (7). Ketoester 5 (83.2 kg, 338 mol) and triethylorthoformate (80.1 kg, 540.7 mol) are heated to reflux (\sim 140 °C) and stirred for 30 min. Acetic anhydride (103.5 kg, 1014 mol) is then added, and heating continued for about 12 h. Then the mixture was cooled and diluted with NMP (210 kg) and acetonitrile (161 kg) and stirred. Water (3.0 kg, 169 mol) is added to the solution, which was then stirred for 10 min to decompose excess triethylorthoformate.

The resulting solution is added to a suspension of 2,6diamino-3,5-difluoropyridine, **6** (57.4 kg, 395 mol), NMP (210 kg), and acetonitrile (161 kg). The reaction typically is complete in <1 h, and the resulting homogeneous solution is added to water (662 kg) over 2 h, precipitating the yellow product. The product is filtered, and the wetcake was washed with a solution of acetonitrile (161 kg) and water (102 kg). The wetcake is then washed with water (600 kg) and dried at 60 °C to provide 120 kg (93%) of the vinylagous amide **7**, as a mixture of *E* and *Z* isomers

Mp 157–160 °C; ¹H NMR (CDCl₃, 300 MHz) (*E*-isomer) δ 1.15 (t, 3H), 4.16 (q, 2H), 4.64 (br s, 2H), 6.90 (m, 1H), 7.22 (t, 1H), 7.32 (m, 1H), 9.03 (d, 1H), 12.44 (bd, 1H); (*Z*-isomer) δ 1.03 (t, 3H), 4.11 (q, 2H), 4.60 (br s, 2H), 6.90 (m, 1H), 7.20 (t, 1H), 7.48 (m, 1H), 8.90 (d, 1H), 11.17 (bd, 1H). Anal. Calcd for C₁₇H₁₂F₅N₃O₃: C, 50.88; H, 3.01; N, 10.47. Found: C, 50.83; H, 2.70; N, 10.32.

1-(6-Amino-3,5-difluoropyridin-2-yl)-6-fluoro-7-(3-isobutyryloxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid, Ethyl Ester, 2c. To a solution of vinylagous amide, 7 (115 kg, 286 mol), LiCl (24.3 kg, 573 mol, 1.99 equiv) in NMP (768.6 kg) is added DBU (46.1 kg, 303 mol, 1.06 equiv) over 1 h 40 min, maintaining the internal temperature at 35 °C. The reaction temperature is then adjusted to 23 ± 5 °C, and the reaction is stirred for 2 h. When the cyclization is complete azetidine hydrochloride (33.9 kg, 309 mol, 1.08 equiv) is added followed by DBU (109.2 kg, 717 mol, 2.5 equiv) over 2 h. The reaction temperature is then adjusted to 23 ± 5 °C. After the addition is complete, isobutyric anhydride (99.7 kg, 630 mol, 2.2 equiv) is added and the reaction is stirred 1 h at 35 °C and

⁽¹⁴⁾ A mechanism in which N-chlorination on the substrate is followed by chlorine transfer to the 8-position is considered unlikely. During the chlorination reactions, we have observed by HPLC compounds which are consumed by the bisulfite quench. Though we have not unequivocally assigned their structures, we believe that they are in fact N-chlorinated byproducts.

⁽¹⁵⁾ Hay, A. M.; Hobbs-Dewitt, S.; MacDonald, A. A.; Ramage, R. Synthesis 1999, 1979–1985.

then cooled to 23 °C, at which point ethyl acetate (104.2 kg) is added. A 10% citric acid solution (570 kg) is added, and the resulting slurry is filtered and washed twice with 115 kg of water. The product is dried at 50 °C to yield 136 kg (93%) of the title product.

Mp 201–209 °C; ¹H NMR (DMSO- d_6 , 400 MHz) δ 8.49 (s, 1H), 8.00 (dd, J = 9.0, 9.3 Hz, 1H), 7.75 (d, J = 12.8 Hz, 1H), 6.79 (br s, 2H), 5.95 (dd, J = 1.5, 7.6 Hz, 1H), 5.21 (m, 1H), 4.36 (t, J = 7.4 Hz, 2H), 4.02 (q, J = 7.0 Hz, 2H), 3.95 (dd, J = 3.7, 9.2 Hz, 2H), 2.58 (hept, J = 7.0 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 6H). Anal. Calcd for C₂₄H₂₃F₃N₄O₅: C, 57.14; H, 4.60; N, 11.11. Found: C, 56.86; H, 4.30; N, 10.89.

1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-isobutyryloxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid, Ethyl Ester, 11. A solution of isobutyrate ester, 2c (101 kg, 198 mol) in dichloromethane (813 kg) at 5 °C is added to a solution of 1,3-dichloro-5,5dimethyl hydantoin, DCH (39.5 kg, 200.5 mol, 1.01 equiv), in dichloromethane (540 kg) cooled to 5 °C over about 1.5 h. The reaction is quenched with cold aqueous sodium bisulfite (50 kg in 500 kg water) over about 1 h, maintaining the temperature at less than 25 °C. The layers are separated, and the organic layer is washed with aq. NaHCO₃ then water. The solution is distilled under a vacuum and then chased with MTBE, during which the product begins to crystallize. After another chase, the product slurry is cooled to 5 °C and isolated by filtration. After drying under a vacuum at 65 °C for 12 h, 109.2 kg (91%) of 11 is isolated. NMR indicated 0.4 equiv of MTBE and 0.4 equiv of CH₂Cl₂.

Mp 103–104 °C. ¹H (CDCl₃/400 MHz) δ 8.35 (s, 1H), 7.95 (d, J = 13.9 Hz, 1H), 7.24 (t, J = 8.4 Hz, 1H), 5.20– 5.16 (m, 1H), 5.12 (bs, 2H), 4.83–4.73 (m, 2H), 4.36 (q, J = 7.1, 2H), 4.40–4.30 (m, 2H), 2.60 (sept, J = 7.0 Hz, 1H), 1.37 (t, J = 7.1 Hz, 3H), 1.19 (d, J = 7.1 Hz, 6H). MTBE: 3.21 (s, 3H), 1.19 (s, 9H). Anal. Calcd for C₂₄H₂₂ClF₃N₄O₅ + 0.4 (C₅H₁₂O) + 0.4 (CH₂Cl₂): C, 51.82; H, 4.55; N, 9.16. Found: C, 51.77; H, 4.33; N, 9.01.

1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3carboxylic Acid (ABT-492), NCS Process: A solution of N-chlorosuccinimide (25.3 kg, 190 mol, 1.03 equiv) in methyl acetate (419 kg) at 17 °C was treated with sulfuric acid (0.56 kg, 5.7 mol, 0.03 equiv). The resulting solution was transferred to a slurry of chloroisobutyrate 11 (92.7 kg, 184 mol) in ethyl acetate (244 kg) at 17 °C. The reaction was quenched/washed with 1.5% aqueous sodium bicarbonate (370 kg), washed with 10% aqueous sodium sulfite (200 kg), and concentrated. The concentrate was dissolved in 2-propanol, treated with 4% (w/w) aqueous potassium hydroxide (750 kg), and stirred at 50 °C until hydrolysis was complete. After filtration, the reaction was treated with 12% aqueous acetic acid (410 kg), and the product was collected by filtration. The filtrant was washed with water and dried at 50 °C to provide 73 kg of product. Mp: 238-241 °C. ¹H NMR (CDCl₃) δ 14.63 (brs, 1H), 8.70 (d, J =0.7 Hz, 1H), 7.95 (dd, J = 9.9, 0.7 Hz, 1H), 7.83 (d, J =13.6 Hz, 1H), 6.75 (s, 2H), 5.75 (d, J = 5.8 Hz, 1H), 4.61 (m, 12H), 4.47 (m, 1H), 4.18 (m, 2H). Anal. Calcd for C₁₈H₁₂ClF₃N₄O₄: C, 49.05; H, 2.74; N, 12.71. Found: C, 48.90; H, 2.48; N, 12.62.

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