Organic Process Research & Development **1997**, *1*, 294−299

Fenleuton: Development of a Manufacturing Process

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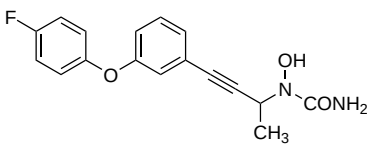
Abstract:

The evolution and development of a commercially viable synthesis of fenleuton, a second-generation 5-lipoxygenase inhibitor, is discussed. Special emphasis is given to the challenges and operational issues encountered on scale-up in the pilot plant. Three separate processes were developed and scaled up, providing valuable information about operational parameters and physical characteristics of the drug substance. A novel displacement reaction was discovered and developed and was incorporated as the key transformation in the final manufacturing process.

Introduction

Inhibition of the 5-lipoxygenase enzyme is known to have therapeutic benefit in the treatment of leukotriene-mediated inflammatory diseases.[1] Abbott Laboratories has developed zileuton,[2] an *N*-hydroxyurea inhibitor successful in blocking the biosynthesis of leukotrienes. Fenleuton[3] (**1**) is a second-generation 5-lipoxygenase inhibitor being developed at Abbott for the treatment of osteoarthritis and related inflammatory diseases in companion animals, especially dogs.

Structurally, fenleuton is a fluoro-substituted diphenyl ether with a butynyl *N*-hydroxyurea side chain. The *R* and *S* enantiomers are considered equally effective, with the former having a longer half-life. The compound is being developed as the racemate.



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In addition to the manufacture of bulk drug to support various clinical programs, our long-term goal was the development and demonstration of a manufacturing process that would be consistent with project cost objectives, manufacturing operations, safety, and environmental concerns. During this development phase, the medicinal chemistry synthesis was scaled up to kilogram scale, and three new processes were developed and successfully scaled up in the pilot plant.

The initial discovery synthesis was scaled up with a few modifications to make the first lot of bulk drug. While adequate for the quantities required by medicinal chemists, this route had serious shortcomings as a scale-up route. Thus, a convergent synthesis was developed to address these concerns and permit scale-up in a reasonably efficient manner. The synthesis, however, involved several purification steps, including recrystallization to meet acceptable limits of purity, and was not considered a cost-effective route. As development continued towards a cost-effective synthesis, the Mitsunobu process was evaluated and scaled up. This process succeeded in yielding high-purity bulk drug without recrystallization. However, in common with the earlier two routes, it utilized the Mitsunobu reaction to incorporate the *N*-hydroxyurea functionality, with its attendant drawbacks of waste byproducts and poor atom efficiency.

A displacement process was an attractive alternative to the Mitsunobu reaction and was projected to be very cost effective. However, significant scale-up issues regarding a key transformation and the physical characteristics of the bulk drug were encountered on scale-up. These had to be resolved in order to realize fully an efficient and high-yielding process.

Results and Discussion

Discovery Synthesis. The initial medicinal chemistry synthesis[3] was a five-step linear synthesis that relied on commercially available starting materials and was readily adapted to the synthesis of analogs for biological evaluation.

The first step of the synthesis was the Cu(I)-mediated Ullman reaction of 3-hydroxybenzaldehyde and 4-bromo-1-fluorobenzene (Scheme 1) to give the adduct **2**, which was reacted under standard Corey−Fuchs conditions to yield the dibromo olefin **3** in high yields. The transformation to the propargylic alcohol **10** was accomplished as a two-step LDA-mediated dehydrohalogenation to the terminal acetylene **4** and the subsequent generation of the acetylide anion and quenching with acetaldehyde. The alcohol upon reaction with *N*,*O*-bis(carbophenoxy)hydroxylamine under Mitsunobu conditions gave the adduct **5**, which was purified by silica (230−400 mesh) chromatography. The final transformation to **1** was achieved by aminolysis.

This initial method was scaled up to make the first kilogram batch of bulk drug. It was observed that the Ullman reaction scaled up poorly, required stoichiometric quantities of CuI, and required 5−7 days for acceptable conversion. The reaction did proceed cleanly, and the desired intermediate **2** could be isolated in 60% yield. The remaining steps

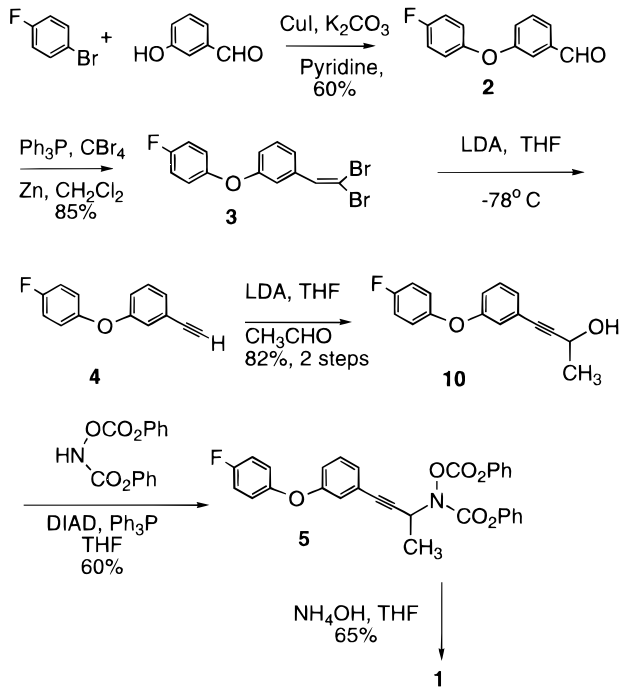
(1) (a) Israel, E. *Ann. Allergy* **1994**, *72*, 279−284. (b) Brooks, D. W. *Expert Opin. Invest. Drugs* **1994**, *3*, 185−190.

(2) (a) Summers, J. B.; Gunn B. P.; Brooks, D. W. U.S. Patent 4873259, Oct 10, 1989. (b) Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R. D.; Bell, R. L.; Summers, J. B.; Brooks, D. W.; Gunn, B. P.; Rubin, P.; Kesterson, J. In *Leukotrienes and Prostanoids in Health and Disease, New Trends in Lipid Mediators Research*; Zor, U., Naor, Z., Danon, A., Eds.; Karger: Basel, 1989; pp 50−55.

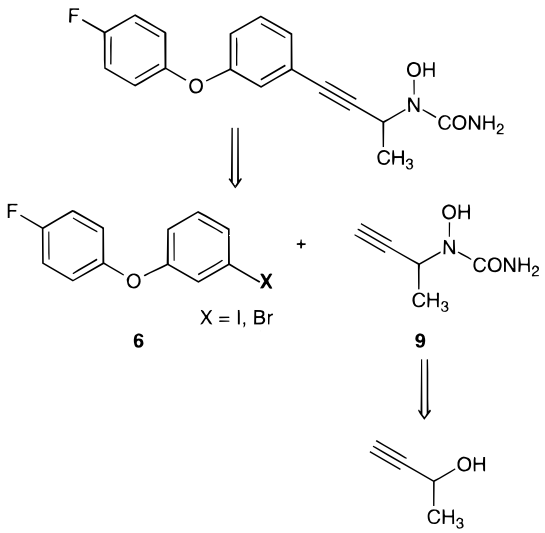
(3) Brooks, D. W.; Stewart, A. O.; Basha, A.; Bhatia, P.; Ratajczyk, J. D. U.S. Patent 5,288,751, Feb 22, 1994.

 S1083-6160(97)00106-0 CCC: $14.00

Scheme 1. **Discovery synthesis**



Scheme 2. **Retrosynthetic analysis**



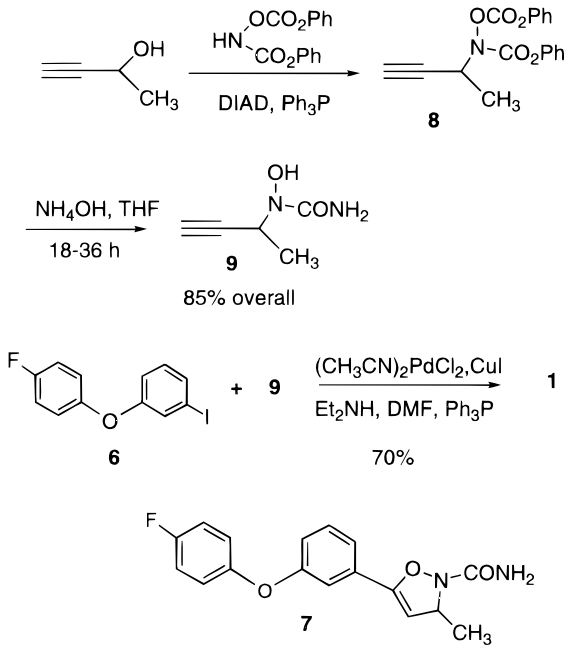
of the synthesis scaled up moderately well, with acceptable purity and an overall yield of 15−18%.

Whereas the chemistry scaled up moderately well, several scale-up issues were encountered. These included the low throughput of the Ullman reaction, column chromatographic purification, and the chromatography wastes and halogenated byproducts that were generated. Operationally, the isolation of all the intermediates, many from incompatible solvents, resulted in a highly inefficient process.

Convergent Synthesis

The retrosynthetic analysis of **1** suggested a convergent synthesis, involving the palladium-mediated coupling reaction[4] of the aryl halide **6** and the acetylenic *N*-hydroxyurea moiety **9** (Scheme 2). The Ullman reaction of 3-iodophenol and 4-bromo-1-fluorobenzene gave the desired product as

Scheme 3. **Convergent synthesis**



well as higher molecular weight side products requiring high-temperature distillation. Outsourcing of **6** proved a success, and several vendors were identified as suppliers.

The availability of **6** allowed the development of a more efficient convergent process to proceed at a rapid pace (Scheme 3). The first step was the Mitsunobu[5] reaction of anhydrous racemic 3-butyn-2-ol with *N*,*O*-bis(carbophenoxy)hydroxylamine,[6] triphenylphosphine, and diisopropyl azodicarboxylate (DIAD). Aminolysis of the adduct **8** resulted in the concurrent deprotection and unmasking of the hydroxyurea functionality, yielding the butynyl *N*-hydroxyurea **9**. The coupling of **6** and **9** was effected in good yields with catalytic amounts of bis(acetonitrile)-palladium(II) chloride, copper(I) iodide, and triphenylphosphine.

The *N*-hydroxyureas are strong chelators of metal ions, and crude fenleuton typically retained significant levels (in the 2000−4000 ppm range) of palladium and copper. Carbon treatment and recrystallization were necessary to decrease heavy metals to the acceptable limit of 20 ppm, with an 80−85% recovery. The yield of pure **1** from **6** was 50−60%.

The convergent synthesis scaled up very well with consistent yields and purity. It was observed that formation of the cyclized byproduct **7** could be minimized by using stoichiometric amounts of base, and diisopropylamine proved to be the most suitable in this regard. The major drawback in this route was the use of heavy metals in the final chemical step. The need for additional purification significantly increased the cost, making this convergent synthesis unsuitable as a long-term commercial manufacturing process.

Anhydrous racemic 3-butyn-2-ol is an expensive reagent, whereas the aqueous 55% solution was commercially available at a fraction of the cost. Thus, developing a process that utilized aqueous butynol became our primary manufacturing strategy. In addition, it was believed that performing

(4) (a) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312.

(5) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(6) Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, *57*, 5020.

Scheme 4. **Mitsunobu process**

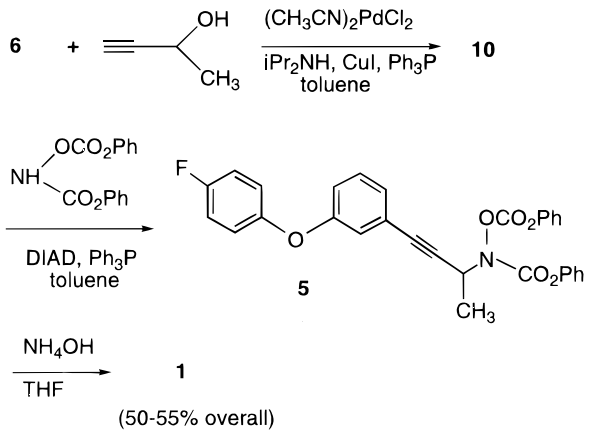
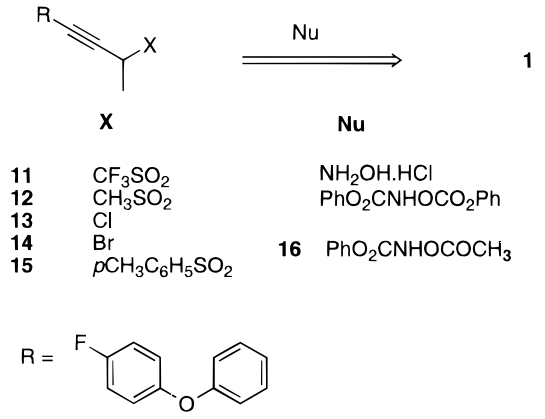


Chart 1. **Displacement substrates and nucleophiles**



the palladium coupling reaction at an earlier stage in the synthesis would result in lower levels of metal impurities at the final step. This would potentially eliminate the need for a purification step.

Mitsunobu Process

The coupling reaction of **6** with 55% aqueous butynol gave the propargylic alcohol **10** in quantitative yield (Scheme 4). The transformation of the alcohol to Fenleuton could be accomplished by the Mitsunobu reaction, or by a displacement reaction with a suitable nucleophile. The first process to be developed from this effort utilized the established Mitsunobu protocol (Scheme 4). The first step of the process was the coupling reaction of the aryl iodide **6** with aqueous butynol in toluene. The solution of the alcohol **10** was then reacted with *N*,*O*-bis(carbophenoxy)hydroxylamine and triphenylphosphine to give the adduct **5**. Addition of a calculated amount of heptane precipitated the triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate byproducts. The mixture was filtered, concentrated, and subjected to aminolysis with ammonium hydroxide and tetrahydrofuran. Crude **1** was purified by slurrying in dichloromethane−heptane mixtures and gave high-purity bulk drug without recrystallization.

The Mitsunobu process was effectively scaled up into multipurpose equipment and was suitable as a manufacturing process. Although the reaction byproducts and waste streams continued to be a concern, the low to moderate commercial volumes of the drug substance permitted its feasibility. However, the development of the displacement process soon paved the way for a more efficient process.

Displacement Process

A large number of displacement substrates and nucleophiles were evaluated as potential components of a conventional S_N2 displacement reaction. Such a process could be expected to form elimination byproducts and have a lower overall yield than the Mitsunobu process. However, the potential benefits of lower cost and decreased waste products were substantial.

As summarized in Chart 1, the propargylic alcohol was converted into its respective sulfonate and halide derivatives. The trifluoromethanesulfonate **11** was found to be unstable. Whereas the methanesulfonate **12** was prepared conventionally, attempts to prepare the *p*-toluenesulfonate ester under standard conditions always resulted in the formation of the chloride **13**. The *p*-toluenesulfonate ester **15** was prepared by using (*p*-tolylsulfonyl)imidazole. The propargylic bromide **14**, a stable crystalline solid, was prepared using conventional brominating agents.

Chart 1 also lists the various nucleophiles evaluated for efficacy in bimolecular displacement reactions. The reactions were conducted in DMF or DMSO with bases such as potassium carbonate or sodium methoxide. It was demonstrated that *O*-acetyl-*N*-carbophenoxyhydroxylamine (**16**), the only nucleophile observed to form the desired product, was not competitive with the Mitsunobu process. It was established, however, that the bromide **14** was the most suitable substrate for this transformation and was converted into fenleuton (**1**) in 37.5% yield.

The application of aqueous 50% hydroxylamine as the nucleophile resulted in the first demonstrable alternative to the Mitsunobu reaction. The reaction of **14** with an excess of aqueous hydroxylamine in refluxing 95% ethanol, followed by reaction of the resulting hydroxylamine **17** with potassium isocyanate in acid medium, gave **1** in 75% yield (two steps, crystallized). This translated to a yield of 50% from the aryl iodide **6** and made this route superior to the Mitsunobu process.

The success of the displacement reaction led to the lab scale demonstration of this process, as shown in Scheme 5. The palladium coupling reaction was conducted in methyl *tert*-butyl ether, and the alcohol **10** was worked up and reacted with phosphorous tribromide.

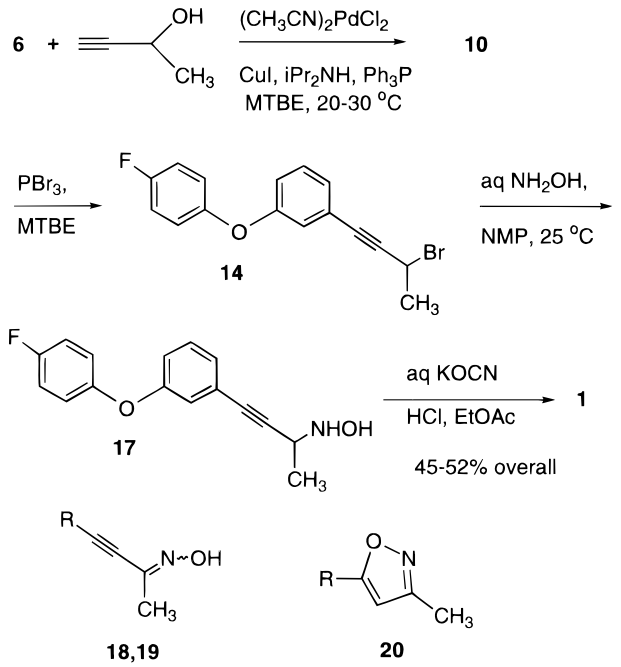
The displacement of the bromide **14** with aqueous hydroxylamine and the subsequent urea formation gave **1** in good overall yield and purity greater than 99%. Residual metal levels were well within acceptable limits and eliminated the need for further purification.

This displacement route resolved the byproduct and waste issues of the Mitsunobu process, utilized inexpensive and commercially available reagents, and was more cost effective. An overall yield of 40% from **6** was deemed essential for this displacement process to be competitive with the Mitsunobu process, and the lab scale runs had demonstrated its feasibility with yields in excess of 50%.

Development Runs

The palladium coupling reaction was quite exothermic, but a rapid and controlled reaction rate could be achieved

Scheme 5. **Displacement process**



by slowly metering in the diisopropylamine and maintaining the reaction temperature below 35 °C. The reaction scaled up very well, and the transformation was virtually quantitative in yield and purity. The bromination and carbamylation reactions also proceeded as expected. However, the scale-up of the displacement reaction was problematic and required a significant modification before the expected results could be realized.

The runs were made on 5−10 kg batches of **6** in 30 and 50 gal glass-lined reactors, and the intermediates were carried through without isolation.

In the first run, an unfavorable impurity profile required a rework involving carbon treatment and recrystallization. It was believed that the impurities resulted from high distillation temperatures during the workup of the displacement reaction and/or the storage of the initially isolated product in a damp condition for several days. However, this was the first scale-up of the key displacement reaction, and the results were deemed a satisfactory demonstration of the displacement process.

In run 2, the distillation of ethanol at the conclusion of the displacement reaction was conducted at lower jacket temperatures. However, this resulted in prolonging the operation significantly, and significant amounts of nonpolar byproducts identified as the oximes **18** and **19**, and the isoxazole **20**, were observed. This resulted in a low overall yield of only 17%, although the desired high purity was realized without any additional purification . It was also noted that the crystal morphology was distinctly different from that obtained in run 1.

It was clear from these results that the hydroxylamine intermediate **17** was not very stable, especially under the high residence times involved in the distillation of ethanol. An extractive workup was evaluated as an alternative to the distillation step.

It was observed that dilution of the reaction mixture with brine and extraction with ethyl acetate did give the expected yields on lab scales. However, the scale-up of this process did not proceed as expected because of poor mixing and other equipment limitations and realized an overall yield of only 25%.

At this stage, it was concluded that ethanol was an unsuitable solvent for the displacement reaction, and a critical reevaluation of this reaction was necessary. Several alternate solvents and reaction conditions were evaluated, with the goals of lower reaction temperatures and ease of workup. This resulted in the discovery that *N*-methyl-2-pyrrolidinone (NMP) was the most suitable solvent, with high conversions and minimal degradation of the hydroxylamine intermediate.

Polymorphism

Two polymorphs, referred to as the "plates" and "needles", were identified. The latter was the form obtained from the earlier processes and is obtained upon recrystallization from ethyl acetate−heptane, ethanol−water, acetone−water, or acetonitrile−water. The plate form was observed only when the product was crystallized directly from the crude ethyl acetate solution of the final reaction mixture, by the addition of heptane. The plate form also exhibited much higher solubility in solvents such as ethyl acetate.

The two crystal forms had similar pharmacokinetic characteristics, and the favored morphology was to be determined by the ease of manufacture. Since recrystallization invariably resulted in the needle form, and any purification step would involve a recrystallization, the needle form was selected as the desired crystal form, and a high-yielding interconversion step had to be developed, which would be consistent with the 40% overall yield for the process.

Conventional purification by recrystallization from ethyl acetate and heptane yielded a recovery of 85−88%. This recovery was unacceptable on a routine basis, and a new recrystallization−interconversion process had to be devised. A mixed solvent system using ethanol−ethyl acetate and heptane−water was developed. Recrystallized yields in excess of 95% were realized, along with the desired morphology and purity, and this "interconversion" was incorporated into the process. The purity of the "crude" compound was >99%, and the purity of the interconverted final product was in the range of 99.5%.

Summary

Process research on the synthesis of fenleuton has resulted in the discovery, development, scale-up, and evaluation of three new processes in the pilot plant. Two of these processes were determined to be commercially viable. The selected process incorporates a novel bimolecular displacement reaction using aqueous hydroxylamine. Several operational and scale-up issues were encountered and resolved, resulting in a cost-effective manufacturing process ready for commercialization.[7]

Experimental Section

Intermediates were not isolated in the Mitsunobu and displacement processes. In-process assays were performed

(7) (a) Chemburkar, S. R.; Patel, H. H.; Sawick, D. P.; Thomas, A. V. Process for the preparation of Arylalkyl-*N*-hydroxyurea derivatives having lipoxygenase inhibitor activity. Process patent filed Sept 12, 1996. (b) Thomas, A. V. Fenleuton: Development of a Manufacturing Process. Hope College Organic Chemistry Symposium, Holland, MI, June 7, 1996.

by thin layer chromatography (silica gel 60 F_{254} 250 μm; eluent, ethyl acetate−heptane mixtures; shortwave UV visualization), or by high-performance liquid chromatography at 230 nm (YMC-PACK ODSA A-303-5, 25 cm × 4.6 mm, 5 μ; mobile phase, 47% acetonitrile, 53% 10 μm pH 3.0 phosphate buffer). Final product assays were in accordance with established Standard Control Procedures.

Convergent Synthesis. *(1) (R,S)-N-Butyn-2-yl-N-hydroxyurea (**9**).* To a suitable vessel were charged triphenylphosphine (1.23 kg, 4.69 mol, 1.2 equiv), *N*,*O*-bis(carbophenoxy)hydroxylamine (1.17 kg, 4.28 mol, 1.1 equiv), and 4 L of tetrahydrofuran. The mixture was stirred to effect dissolution, and anhydrous DL-3-butyn-2-ol (0.27 kg, 3.85 mol) was added. The solution was cooled to 0−10 °C, and diisopropyl azodicarboxylate (0.87 kg, 4.3 mol, 1.1 equiv) was slowly added. The mixture was stirred for 1 h at 0−10 °C, 4 L of 28% ammonia water was then added, and the biphasic mixture was vigorously agitated for 18 h. The tetrahydrofuran was distilled under vacuum, and the precipitated triphenylphosphine oxide and diisopropyl hydrazinedicarboxylate was filtered off. The aqueous filtrate was extracted with toluene (3 × 4 L). The aqueous phase was saturated with solid sodium chloride and extracted with ethyl acetate (5 × 4 L). The ethyl acetate fractions were concentrated to 2.5 L and diluted with 10 L of heptane to precipitate **9**. Yield: 0.398 kg, 80%. IR (cm^{-1}): 3450, 3285, 1655, 1580, 1450.

*(2) N-Hydroxy-N-[4-(3-(4-fluorophenoxy)phenyl)-3-butyn-2-yl]urea (**1**).* A suitable vessel was charged with the aryl iodide **6** (0.4 kg, 1.27 mol), acetylenic *N*-hydroxyurea **9** (0.17 kg, 1.34 mol, 1.05 equiv), triphenylphosphine (0.0064 kg, 0.024 mol, 1.9 mol %), copper(I) iodide (0.0012 kg, 0.0065 mol, 0.5 mol %), 150 mL of diethylamine, and 1.4 L of dimethylformamide. The mixture was maintained at 20−25 °C, bis(acetonitrile)palladium(II) chloride (0.0033 kg, 0.0127 mol, 1.0 mol %) was added, and the mixture was stirred for 18 h. The mixture was diluted with 16 L of water, and the precipitated product was washed with water and heptane and allowed to air dry.

The crude material was slurried with 600 mL of a 25% v/v dichloromethane−heptane mixture and filtered, and the filter cake was washed with a 50% v/v dichloromethane−heptane mixture until the filtrate ran clear (1.4 L). The filter cake was dried, to yield 339 g of product. It was dissolved in 2.5 L of ethyl acetate at 50−55 °C, and the solution was treated with 85 g of Norit A carbon and filtered. The filtrate was diluted with 4.5 L of heptane. The precipitated product was collected and dried under vacuum at 40 °C for 8 h, to yield 278 g. The purified product was dissolved in 1.1 L of tetrahydrofuran at 20−25 °C, the solution was slurried with 27.5 g of Norit A carbon, and the slurry was filtered. The filtrate was diluted with 6 L of deionized water, and the product was collected and dried under vacuum at 40 °C. Yield: 244 g (61% from **6**). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (d, 3H), 5.1 (q, 1H), 6.5 (bs, 2H), 6.85−7.42 (m, 8H), 9.3 (s, 1H).

Mitsunobu Process. *(3) 4-[3-(4-Fluorophenoxy)phenyl]-3-butyn-2-ol (**10**).* A 30 gal glass-lined reactor was charged with **6** (6.5 kg, 20.70 mol), 55% aqueous 3-butyn-2-ol (3.2 kg, 25.11 mol, 1.2 equiv), and 18 kg of toluene and cooled to 0−10 °C. To the solution were added diisopropylamine (2.5 kg, 24.71 mol, 1.2 equiv), copper(I) iodide (0.0394 kg, 0.21 mol, 1 mol %), triphenylphosphine (0.059 kg, 0.23 mol, 1.1 mol %), and bis(acetonitrile)palladium(II) chloride (0.027 kg, 0.10 mol, 0.5 mol %). The mixture was agitated for 2 h and then quenched by the addition of 8 kg of 28% ammonia water and 30 kg of brine. The organic phase was successively washed with 35 kg of brine, 12 kg of 10% hydrochloric acid, 12 kg of 10% sodium bicarbonate, and 20 kg of brine. The organic phase was then slurried with 1 kg of anhydrous magnesium sulfate, 0.7 kg of PWA carbon, and 0.7 kg of Ultra Norit C carbon for 2 h. The solution was filtered, the filter cake was washed with 2.5 kg of toluene, and the toluene phases were combined.

*(4) N,O-Bis(carbophenoxy)-N-[4-(3-(4-fluorophenoxy)-phenyl)-3-butyn-2-yl]hydroxylamine (**5**).* The reactor was charged with the toluene solution of **10**, triphenylphosphine (6.2 kg, 23.66 mol, 1.1 equiv), and *N*,*O*-bis(carbophenoxy)-hydroxylamine (6.2 kg, 22.71 mol, 1.1 equiv), and cooled to 0−5 °C. To the cooled solution was added diisopropyl azodicarboxylate (4.8 kg, 23.74 mol, 1.1 equiv), the reaction temperature being maintained below 10 °C. After 2 h, the conversion was complete, and heptane (1.5 × calculated volume of toluene) was added. The precipitated solid byproducts were filtered off. The solids were slurried with 1:1.5 v/v toluene−heptane, the slurry was filtered, and the combined filtrate and washes were concentrated.

*(5) N-Hydroxy-N-[4-(3-(4-fluorophenoxy)phenyl)-3-butyn-2-yl]urea (**1**).* The concentrate of **5** was dissolved in 10 kg of THF and agitated vigorously with 35 kg of 28% ammonia water for 60 h. The mixture was diluted with 100 kg of water and 20 kg of heptane, and the precipitated product was filtered off. Crude **1** was slurried with 24 kg of 25% v/v dichloromethane−heptane at 20−25 °C and the slurry filtered. The wet cake was slurried with 20 kg of dichloromethane at 20−25 °C, the slurry filtered, and the filter cake washed with chilled dichloromethane and heptane. The product was dried under vacuum at 40−45 °C for 12 h, to give 3.1 kg of **1**, 47.7% overall yield from **6**.

Displacement Process. *(6) 4-[3-(4-Fluorophenoxy)-phenyl]-3-butyn-2-ol (**10**).* A 30 gal glass-lined reactor was charged with **6** (6.0 kg, 19.1 mol), triphenylphosphine (0.055 kg, 0.21 mol, 1.1 mol %), copper(I) iodide (0.037 kg, 0.19 mol, 1 mol %), bis(acetonitrile)palladium(II) chloride (0.025 kg, 0.096 mol, 0.5 mol %), and 25 kg of *tert*-butylmethyl ether. The mixture was stirred to dissolve the solids, and 55% aqueous 3-butyn-2-ol (2.7 kg, 20.87 mol, 1.1 equiv) was added. Diisopropylamine (2.1 kg, 20.75 mol, 1.1 equiv) was added over a period of 40 min, the reaction temperature being maintained between 15 and 30 °C. The mixture was stirred for an additional 2 h and quenched with 12 kg of 28% ammonia water. Saturated sodium chloride solution (15 kg) was added, and the layers were mixed and separated. The organic phase was cooled to 5−10 °C and washed with 10% aqueous hydrochloric acid. The organic phase was washed with 10% sodium bicarbonate and brine and dried by filtration through a pad of anhydrous magnesium sulfate (KF = 0.0%). ^{1}H NMR ($CDCl_3$): δ 1.53 (d, 3H), 1.87 (d, 1H), 4.73 (dq, 1H), 6.92−7.30 (m, 8H). MS: 256 $(M)^+$, 239 $(M - OH)^+$.

*(7) 2-Bromo-4-[3-(4-fluorophenoxy)phenyl]-3-butyne (**14**).* Phosphorous tribromide (5.2 kg, 19.2 mol, 1.0 equiv) was added to the solution of the alcohol **10** in MTBE, the reaction temperature being maintained at 20−30 °C. After 3 h, the mixture was cooled to 5 °C, and 20 kg of distilled water was slowly added. The layers were separated, and the organic layer was washed with distilled water and aqueous potassium carbonate. The organic phase was concentrated under vacuum and used directly in the subsequent reaction. ^{1}H NMR (300 Mhz, $CDCl_3$): δ 1.98 (d, 3H), 4.83 (q, 1H), 6.94−7.30 (m, 8H). MS: 318, 320 $(M + H)^+$, 239 $(M - Br)^+$.

*(8) N-[4-(3-(4-Fluorophenoxy)phenyl)-3-butyn-2-yl]hydroxylamine (**17**).* *N*-Methyl-2-pyrrolidinone (30 kg) was added to the residue and mixed to dissolve all the solids, and 12 kg of 50% aqueous hydroxylamine (181.82 mol, 9.5 equiv) was added. The mixture was agitated at 25 °C for 2.5 h and then quenched with 16 kg of 10% aqueous sodium bicarbonate solution. The mixture was diluted with 26 kg of ethyl acetate and 16 kg of brine. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The organic layers were combined and held at 0−5 °C for the final step. ^{1}H NMR ($CDCl_3$): δ 1.42 (d, 3H), 4.05 (q, 1H), 5.33 (br, 1H), 6.91−7.28 (m, 8H). MS (FAB): 272 $(M + H)^+$, 239 $(M - NHOH)^+$. MS (DCI/NH_3): 289 $(M + NH_4)^+$, 543 $(2M + H)^+$.

*(9) N-Hydroxy-N-[4-(3-(4-fluorophenoxy)phenyl)-3-butyn-2-yl]urea (**1**).* A solution of potassium isocyanate (3.1 kg, 38.21 mol, 2.0 equiv) in 18 kg of water was added to the reactor, and the contents were cooled to 0−5 °C. Concentrated hydrochloric acid (4.7 kg) was slowly added, the temperature being maintained at 0−10 °C. The reaction was quenched after 1.5 h with 23 kg of sodium bicarbonate solution. The layers were separated. To the organic layer were added 25 kg of distilled water and 75 kg of heptane. Crystallization was allowed to proceed for 1 h, and the solids were filtered off. The filter cake was washed successively with 20 kg of distilled water, 6.0 kg of chilled 25% v/v ethyl acetate in heptane, and 14.0 kg of heptane. A 1.0 kg portion of the filter cake, the plate crystal form, was dried in a tray dryer under vacuum at 40 °C. The balance (3.0 kg) was held for interconversion to the needle crystal form (approximate yield: 3.1 kg, 51.7% overall).

Interconversion. The wet cake was dissolved in 13.1 kg of 30% w/w ethyl alcohol in ethyl acetate. Distilled water (30 kg) and 12.7 kg of heptane were added, and the mixture was agitated for 1.5 h. The product was filtered, and the filter cake was washed with 10 kg of distilled water and 15 kg of heptane. The product was dried in a tray dryer at 40−45 °C. Yield of **1**, needle crystals: 2.1 kg (ca. 88% recovery). Note: Drying the product prior to interconversion gives a recovery of 95−96%.

Received for review April 16, 1997.[⊗]

OP970106N

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.