Organic Process Research & Development **1997**, *1*, 137–148

Chemical Development of a Pilot Scale Process for the ACAT Inhibitor 2,6-Diisopropylphenyl [(2,4,6-Triisopropylphenyl)acetyl]sulfamate

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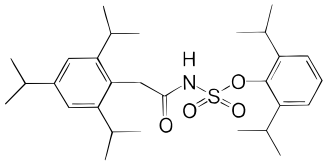
Abstract:

A manufacturing process to prepare the ACAT inhibitor 2,6-diisopropylphenyl [(2,4,6-triisopropylphenyl)acetyl]sulfamate (1; CI-1011) has been developed and successfully demonstrated on a pilot scale. Commercially available 1,3,5-triisopropylbenzene (9) was chloromethylated to give 2,4,6-triisopropylbenzyl chloride (8). Cyanation of 8 under phase-transfer-catalyzed conditions followed by basic hydrolysis of the intermediate and nonisolated 2,4,6-triisopropylbenzyl cyanide (7) gave 2,4,6-triisopropylphenylacetic acid (2), a key intermediate in the convergent synthesis of 1. Commercially available 2,6-diisopropylphenol (12) was converted to [(2,6-diisopropylphenyl)-oxy]sulfonyl isocyanate (13) when reacted with chlorosulfonyl isocyanate under thermodynamically controlled conditions. Hydrolysis and decarboxylation of 13 *in situ* gave 2,6-diisopropylphenyl sulfamate (3), the other key intermediate. A robust process to couple 2 and 3 was developed *via* the intermediacy of (2,4,6-triisopropylphenyl)acetyl chloride (15) to give the final pharmaceutical product that met specifications for clinical and toxicological use. Cost, operational, safety, environmental, and equipment considerations were taken into account during the course of development.

Introduction

The continued search for new drug therapies to treat hypercholesterolemia and atherosclerotic disease has led to the development of compounds that are inhibitors of acyl coenzyme A:cholesterol acyltransferase (ACAT). There is evidence that this enzyme is important in the absorption of dietary cholesterol from the intestine, the secretion of very low density lipoproteins by the liver, and the esterification of cholesterol and storage of the esters in the arterial wall.[1] Inhibitors of this enzyme therefore not only may lower plasma cholesterol but also may reduce the severity of arterial lesions.[2] A series of recently reported *N*-acyl sulfamic acid esters, *N*-acyl sulfonamides, and *N*-sulfonyl carbamic acid esters have been shown to be potent ACAT inhibitors *in vitro* and possess excellent lipid-lowering activity *in vivo*.[3] In particular, 2,6-diisopropylphenyl [(2,4,6-triisopropylphenyl)-acetyl]sulfamate (CI-1011, **1**) has demonstrated superior efficacy in animal models and is being developed as a hypercholesterolemic and antiatherosclerotic agent.[4]



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During the course of the development of **1** as a new drug entity, the material demand for the bulk drug substance steadily escalated from gram amounts to multiple kilogram quantities. The support of toxicological studies of continually lengthening duration, the development of a formulation for the final dosage form, and the preparation of clinical supplies specifically resulted in requests for significant quantities of **1**. For this reason, a chemical process for **1** was required that could at least be implemented on a pilot scale to meet the material demands for drug development, and which preferably could also be transferred to a manufacturing setting if the compound was to go into full scale production.

This paper describes the progress we have made towards the development of a manufacturing process for **1**. The chemical development presented here begins with relatively minor process improvements made to the original synthetic method in order to prepare the first kilogram of **1**. More significant changes are made during the development of the process to be conducted on a pilot scale to prepare multiple kilogram amounts, in particular, the choice of a synthetic route based on the commercial availability of raw materials. Further process development work takes into account cost, safety, environmental, and equipment considerations. Also included here are a number of process differences that were observed during scale-up of the process from the laboratory to the pilot plant.

Results and Discussion

The first and most obvious step in the retrosynthetic analysis of compound **1** involves the disconnection of the C−N amide bond to give the two fragments **2** and **3** (Figure 1). Both the original discovery route to compound **1** and the large-scale preparative process subsequently developed adopted this approach. The development of a process for compound **1** thus came down to the development of individual processes for 2,4,6-triisopropylphenylacetic acid (**2**) and 2,6-diisopropylphenyl sulfamate (**3**), two intermedi-

(1) Sliskovic, D. R.; Trivedi, B. K. *Curr. Med. Chem.* **1994**, *1*, 204.
(2) Bocan, T. M. A.; Bak Mueller, S.; Uhlendorf, P. D.; Newton, R. S.; Krause, B. R. *Atherosclerosis* **1993**, *99*, 175.
(3) (a) Roark, W. H.; Roth, B. D.; Holmes, A.; Trivedi, B. K.; Kieft, K. A.; Essenburg, A. D.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1993**, *36*, 1662. (b) Roth, B. D.; Roark, W. H.; Picard, J. A.; Stanfield, R. L.; Bousley, R. F.; Anderson, M. K.; Hamelehle, K. L.; Homan, R.; Krause, B. R. *Bioorg. Med. Lett.* **1995**, *5*, 2367. (c) Picard, J. A.; O'Brien, P. M.; Sliskovic, D. R.; Anderson, M. K.; Bousley, R. F.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1996**, *39*, 1243.
(4) Lee, H. T.; Picard, J. A.; Sliskovic, D. R.; Wierenga, W. US 5,491,172, Feb 13, 1996.

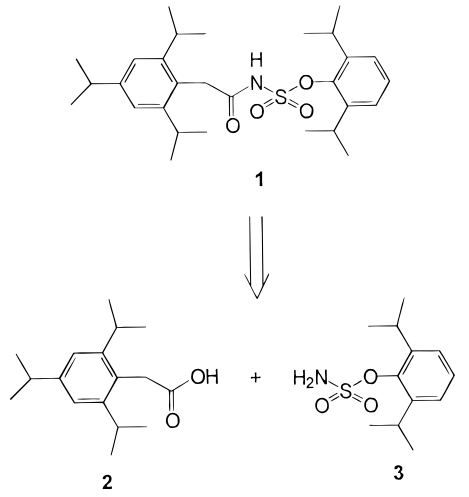
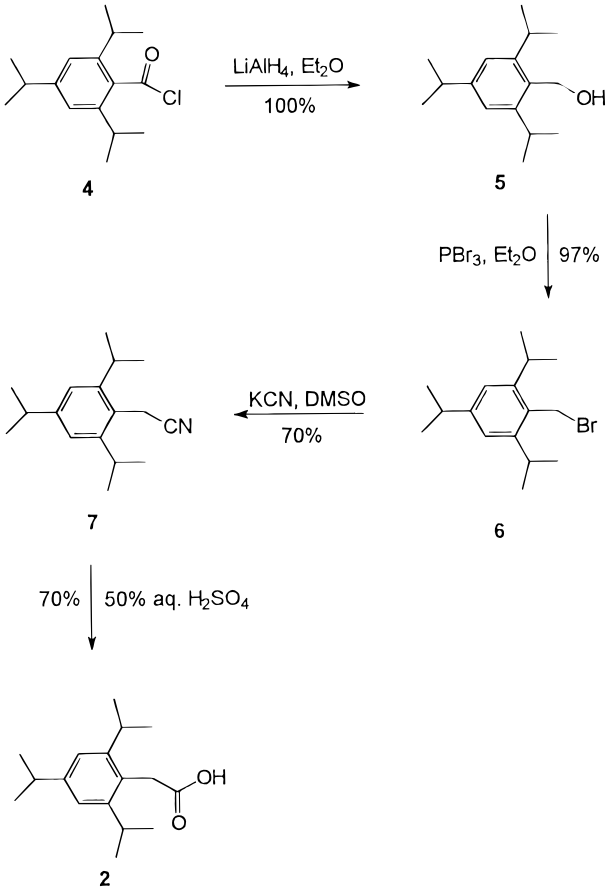


Figure 1. **Retrosynthetic analysis.**

Scheme 1. **Discovery synthesis of 2**



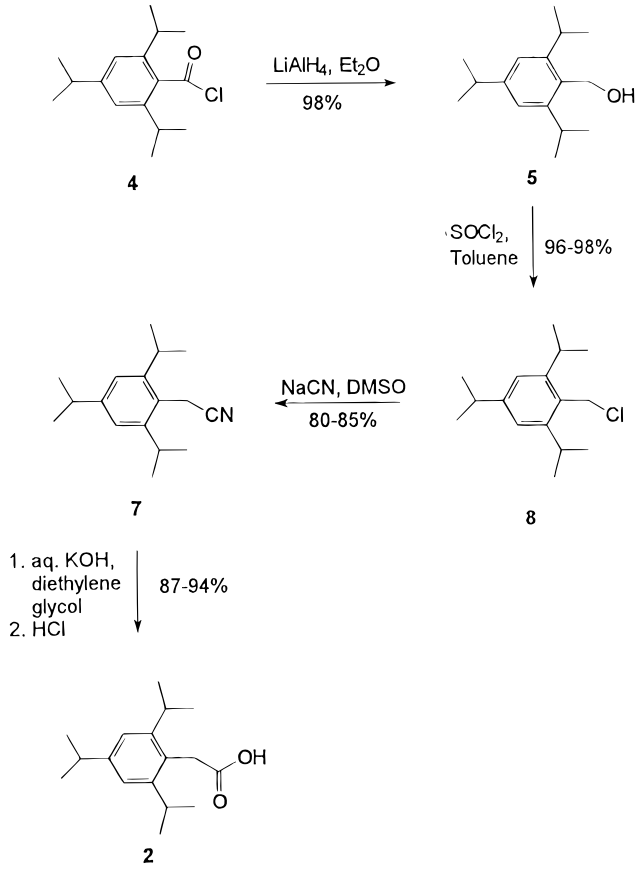
ates which could then be coupled together in a convergent synthesis of **1**. The following sections describe the development of pilot scale processes for these intermediates and a pilot scale process for their combination to form the final pharmaceutical product.

Development of a Process for 2,4,6-Triisopropylphenylacetic Acid. The synthetic route used to make the first gram quantities of acid **2** is shown in Scheme 1. Benzyl alcohol **5**, obtained from the reduction of commercially available 2,4,6-triisopropylbenzoyl chloride (**4**), was converted to the corresponding benzyl bromide **6**. Cyanide displacement followed by acid hydrolysis of **7** gave the desired phenylacetic acid **2**.[4]

Apart from chromatographic purification of both **6** and **2** and the extensive use of extractions in the workup procedures, the discovery synthesis of **2** presented a number of problems concerning longer term development and the production of larger quantities of **2** on a pilot scale. Firstly, the commercial availability of multiple kilogram quantities of the starting acid chloride **4** was an issue. The compound had to be custom made; it was also very expensive. Significantly, the acid chloride functionality was required for the subsequent reduction to occur. Reaction of the relatively more accessible substrate, 2,4,6-triisopropylbenzoic acid, under similar conditions resulted in only a trace of the desired benzyl alcohol **5** being produced. Secondly, the synthesis utilized several hazardous reagents which would require special handling precautions if used on a pilot scale. The extremely reactive lithium aluminum hydride (LAH) and the toxic potassium cyanide/DMSO mixture fell into this category. The elimination of the volatile and highly flammable diethyl ether would also be a desirable feature of any new process. Thirdly, large amounts of phosphates and sulfates in the waste streams from the phosphorous tribromide and acid hydrolysis reactions posed a local disposal problem. Before these aqueous waste streams could be disposed of, both phosphates and sulfates would have to be precipitated as their calcium salts and filtered off. Finally, the acid hydrolysis of **7** to **2** presented an equipment safety problem. Under the conditions employed, the free acid **2** sublimed out of the reaction mixture and crystallized on the cooler parts of the equipment. This could create a potentially dangerous situation in a pilot plant setting where blockage of the heat exchanger or the vent line by solids could lead to a pressure buildup in the reactor.

During the first stages of development, research was concentrated on modifying the reagents used in the synthesis rather than on a change in synthetic route. This was done primarily to accelerate the production of the first few kilograms of compound **1** and to simplify practical manipulation on a relatively large laboratory scale. The modified sequence is shown in Scheme 2. Since the commercial supply of acid chloride **4** was sufficient to meet the short-term material demands for the final pharmaceutical product, its use as a raw material for **2** was continued. Also, as the yield and quality of the product from the LAH reduction in diethyl ether were excellent, it was decided that this reaction be used again to produce alcohol **5** on up to a 500 g scale of **4**. The use of LAH was likely to be eliminated in the long term, as an alternative raw material to acid chloride **4** would eventually have to be sought. Inferior yields in the reduction step were obtained when THF was used as the solvent in place of diethyl ether, due to the product alcohol being solubilized in the aqueous phase by THF. In the reaction to form the substrate for the cyanide displacement, phosphorous tribromide in diethyl ether was replaced with thionyl chloride in toluene to give the corresponding benzyl chloride **8**. The use of thionyl chloride in experiments run on a scale of up to 388 g of **5** gave rise to fewer impurities and a less colored product. It also eliminated the need for an aqueous workup procedure. Instead, excess thionyl chloride and toluene were removed under moderate vacuum and the residual oil was distilled under high vacuum to give **8** in both high yield and

Scheme 2. **Initial development of the process for intermediate 2**

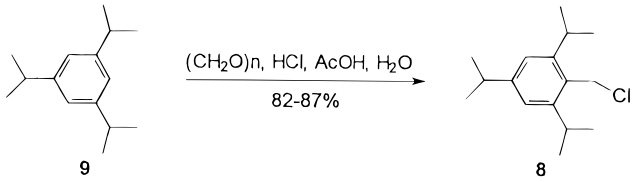


high purity. Following a procedure similar to that reported in the literature,[5] benzyl chloride **8** was converted to nitrile **7** in 80−85% yields on a scale of up to 800 g of **8**. The method used sodium cyanide as a replacement for the more expensive potassium cyanide and involved quenching the reaction mixture into water to give a highly filterable crude product, thereby eliminating the extractive isolation procedure used previously. The crude material was purified very effectively by recrystallization from hot hexane. DMSO was found to be far superior to aqueous ethyl alcohol as the solvent for the displacement reaction in terms of throughput, product color, and chemical yield (20% greater). In order to avoid the sublimation of acid **2** during the hydrolysis of **7**, strongly basic reaction conditions[5,6] were used to give the corresponding potassium salt of acid **2**. The reaction medium consisted of potassium hydroxide in diethylene glycol containing a small amount of water. A reaction temperature of greater than 140 °C for 16 h was necessary to convert the rapidly formed primary amide intermediate into the desired salt. The corrosive nature of the mixture caused severe etching of glass flasks, so the reaction was generally run in stainless steel equipment. The hydrolysis gave 87−94% yields of excellent purity acid **2** and was successfully scaled up to produce up to 600 g of **2** in the laboratory.

During the second stage of the development of a process for compound **2**, a new synthetic route was sought that began with a commercially more accessible raw material. In the

(5) Rand, L.; Mohar, A. F. *J. Org. Chem.* **1965**, *30*, 3885.
(6) Fuson, R. C.; Armstrong, L. J.; Shenk, W. J. *J. Am. Chem. Soc.* **1944**, *66*, 964.

Scheme 3. **Chloromethylation of 1,3,5-triisopropylbenzene**



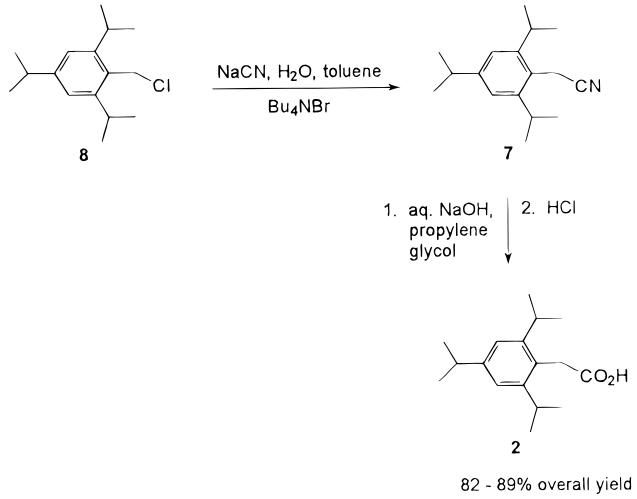
route developed, 1,3,5-triisopropylbenzene (**9**), a commercially available and inexpensive processing solvent, was chloromethylated to give benzyl chloride **8** (Scheme 3). Utilizing features from the reported procedures for the chloromethylation of **9**[7] and mesitylene,[8] the process used paraformaldehyde, hydrochloric acid, and hydrogen chloride gas as reagents and acetic acid as the reaction solvent. The chloromethylation was conducted at 75 °C, and hydrogen chloride gas was charged periodically over several days to increase the degree of conversion of **9** to **8**. Typically, the reaction was stopped when there was less than 2% of **9** remaining. The crude product separated from the aqueous acetic acid phase and was fractionally distilled under high vacuum to give 82−87% yields of **8** on up to a 700 g scale of **9**. The main product fraction collected contained unreacted **9** as the major impurity, but this was found to be removed during the subsequent processing steps. The low-boiling fractions from the distillation, which were more enriched in **9**, were recyclable and could be mixed with fresh **9** in new chloromethylation reactions.

The drawback of any chloromethylation process, however, is the hazard posed by bis(chloromethyl) ether (BCME), a potent human carcinogen and a potential byproduct from the reaction. For this reason, the chloromethylation process to prepare compound **8** was transferred to a custom manufacturer that specializes in chloromethylations and has the required safety procedures in place. The process was successfully scaled up to produce 40 kg batches of excellent quality benzyl chloride **8**. Levels of BCME in the product were measured at less than 0.1 ppb and were deemed acceptable for subsequent handling.

The development of the chloromethylation process had solved the raw material availability problem and had provided sufficient amounts of **8** for the next stage of development, which was the design of a more streamlined process for the pilot scale conversion of **8** into phenylacetic acid **2** (Scheme 4). The first step, the cyanation of **8** to give nitrile **7**, appeared to be an ideal candidate for phase-transfer-catalyzed chemistry.[9] The phase-transfer-catalyzed procedure developed used tetra-*n*-butylammonium bromide (1.5% by weight) as the catalyst and a toluene/water system to solubilize both benzyl chloride **8** and sodium cyanide. Water had the additional benefit of being a far safer medium for both the handling and disposal of cyanide. The reaction proceeded both rapidly and exothermically when the mixture was heated above 60 °C. This reaction being a transfer-rate-limited reaction,[9] the batch temperature could be controlled, if necessary, by adjustment of the rate of agitation.

(7) Bollag, W.; Ruegg, R.; Ryser, G. US 4,105,681, Aug 8, 1978.
(8) Fuson, R. C.; Rabjohn, N. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 557.
(9) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994.

Scheme 4. **Pilot scale process for intermediate 2**

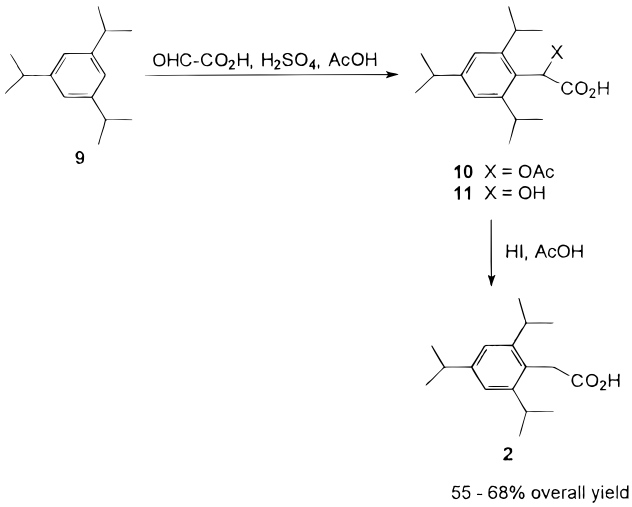


The reaction was run at a high throughput of 1 kg of **8**/L of toluene, and due to the increased nucleophilicity of the cyanide ion under the phase-transfer conditions, the sodium cyanide charge was reduced from 1.7 to 1.05 equiv, thereby greatly reducing the amount of cyanide in the waste stream. The reaction had the additional benefits of being essentially quantitative, generating very little color, and giving rise to only trace amounts of new impurities. Indeed, the quality of the crude nitrile was sufficiently high that the separate isolation, drying, and purification steps used previously for **7** were no longer necessary, enabling the toluene solution of **7** to be used directly in the hydrolysis step.

For this reaction, propylene glycol was added to the toluene solution of **2** and toluene was distilled out of the mixture under vacuum. Propylene glycol was substituted for diethylene glycol since, in contrast to the latter solvent, propylene glycol is nontoxic yet still has a boiling point sufficiently high to meet the requirement of this particular nitrile hydrolysis reaction. A 70% aqueous sodium hydroxide solution was used for the hydrolysis in place of the slightly more expensive potassium hydroxide solution. Again, due to the strongly caustic nature of the mixture and the high reaction temperature required, the reaction was conducted in stainless steel equipment. For the removal of colored impurities from the crude product, a methyl alcohol solution of the acid was treated with activated carbon before the addition of water to crystallize acid **2**. From benzyl chloride **8**, overall yields of 91−95% of excellent quality product were routinely obtained in the laboratory. When the process was run in the pilot plant on a 40 kg scale of **8**, slightly lower yields were obtained. This was attributed to the increased levels of activated carbon that were required to produce material having acceptable color. On a pilot scale, noticeably darker reaction mixtures were generated during hydrolysis in the stainless steel reactor.

A non-chloromethylation route to acid **2** from 1,3,5-triisopropylbenzene was simultaneously developed and demonstrated on a laboratory scale. This route was pursued to provide an alternative and potentially less costly synthesis of **2**. The procedure involved the acid-catalyzed hydroxyalkylation of **9** using glyoxylic acid followed by the hydriodic acid reduction of the mixture of intermediate α-hydroxy- and α-acetoxyphenylacetic acids **10** and **11** (Scheme 5).

Scheme 5. **Glyoxylic acid hydroxyalkylation and hydriodic acid reduction of 1,3,5-triisopropylbenzene**



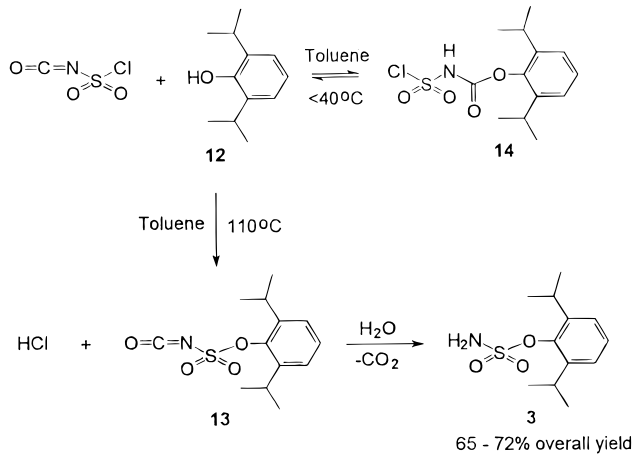
The process was developed on the basis of reported methods for the hydroxyalkylation of aromatic hydrocarbons using alkyl glyoxylates,[10] the hydriodic acid reduction of benzylic alcohols,[11] and the preparation of other substituted phenylacetic acids using a similar synthetic approach.[12] The process has a number of attractive features from an operational point of view. Firstly, with acetic acid being the common solvent for both chemical steps, the reaction could be performed in a single vessel with the sequential addition of reagents. Secondly, a novel triphasic extraction formed part of the workup procedure in which the sodium salt of the product acid **2** was sandwiched between an upper toluene layer and a lower aqueous layer. This permitted effective purification of the product from unreacted **9** and inorganic salts.

The main byproduct of the hydriodic acid reduction was iodine. Since this had a tendency to sublime out of the flask and condense on the cooler parts of the equipment, the second step was conducted in a sealed system. The iodine was subsequently destroyed by reduction with sodium metabisulfite. All attempts to reduce the mixture of **10** and **11** by catalytic hydrogenation gave only trace amounts of **2** even with high pressures, temperatures, and catalyst loadings.

The overall yield for the process on a laboratory scale, after the standard recrystallization procedure for acid **2**, was 55−68%. With the yield for the reduction step being essentially quantitative, the overall yield reflects the relatively moderate conversion achieved in the first step. The conversion was found to be dependent on the relative stoichiometry between **9** and glyoxylic acid, the number of equivalents of sulfuric acid, and the water content, and it was eventually optimized at 65−70% with unreacted **9** constituting the majority of the remaining mass balance. The reaction proceeded to the greatest extent in the presence of approximately 1 equiv of water, which could be introduced by

(10) Werber, G.; Buccheri, F. *Gazz. Chim. Ital.* **1966**, *96*, 465.
(11) (a) Fuson, R. C.; Armstrong, L. J.; Chadwick, D. H.; Kneisley, J. W.; Rowland, S. P.; Shenk, W. J.; Soper, Q. F. *J. Am. Chem. Soc.* **1945**, *67*, 386. (b) Parham, W. E.; Sayed, Y. A. *Synthesis* **1976**, 116.
(12) (a) Kaniss, N.; Bauer, A. US 4,329,497, May 11, 1982. (b) Christidis, Y.; Vallejos, J.-C. US 4,515,970, May 7, 1985. (c) Spielmann, W.; Schaeffer, G. US 4,590,295, May 20, 1986.

Scheme 6. **Pilot scale synthesis of intermediate 3**



the use of glyoxylic acid monohydrate as the reagent for the hydroxyalkylation. However, due to the significantly lower cost of 50% aqueous glyoxylic acid, the latter reagent was used and excess water removed by codistillation with acetic acid prior to the charging of **9** and sulfuric acid.

Development of a Process for 2,6-Diisopropylphenyl Sulfamate. The process first used to prepare sulfamate **3** is shown in Scheme 6 and was similar to that described in the literature.[13] Commercially available 2,6-diisopropylphenol was treated with chlorosulfonyl isocyanate (CSI) in toluene at reflux to give isocyanate **13**. After removal of solvents, **13** was quenched into water, where it underwent hydrolysis and decarboxylation to sulfamate **3**. The crude product was isolated and purified by recrystallization.

The reaction between phenol **12** and CSI can give rise to two different products depending on the reaction temperature.[13,14] When the two reagents are mixed in toluene at ambient temperature, as is done in the initial charging procedure, carbamate **14** is formed. Under these kinetically controlled conditions, phenol **12** attacks the most reactive site on the CSI molecule, the isocyanate group, to give the corresponding adduct. This addition reaction is reversible, however, and upon heating to the reflux temperature of toluene, the thermodynamically more stable isocyanate **13** is formed together with hydrogen chloride gas, which is irreversibly lost from the system. Consequently, after a period of 12−16 h at this temperature, all of compound **14** has been converted to intermediate **13**.

The process described above was successfully performed in the laboratory up to a scale of 700 g of 2,6-diisopropylphenol to consistently produce 65−72% yields of excellent purity 2,6-diisopropylphenyl sulfamate (**3**). However, during the course of the first pilot plant demonstration run on a 12 kg scale of 2,6-diisopropylphenol (**12**), it became obvious that major differences were occurring from the behavior expected on the basis of previous laboratory experience. Firstly, the intermediate isocyanate **13**, after removal of solvents, was a dark brown color instead of being light yellow. The oil also contained solid deposits, which had never been observed previously. Secondly, following the aqueous quench procedure and isolation, the crude product was found to assay at only 75% by weight instead of at the typical value of around 95%. Additionally, the crude material was contaminated with polar UV-active impurities that again had not been detected in laboratory scale batches. In order to produce white to off-white colored sulfamate **3** having acceptable purity, the crude product had to be recrystallized twice with two accompanying activated carbon treatments. As a result of the extra purification steps necessary, only a 32% yield of **3** was obtained, approximately half that expected. An extensive investigation was undertaken to determine the origin of the low yield and poor quality material produced in the pilot scale reaction. The first problem discovered was the result of an equipment compatibility issue. A chemical interaction had occurred between CSI and the phenolic resin used as a binder for the graphite material from which the heat exchanger on the reactor was constructed. During the 12−16 h reflux period this interaction had caused degradation of the graphite heat exchanger, giving rise to the solid residues observed in the isocyanate **13**. Products from this degradation also gave rise to the polar UV-active impurities detected in the crude sulfamate **3**. The degradation of the heat exchanger obviously had significant safety implications, particularly if the integrity of the heat exchanger were ever compromised and coolant were to leak into the CSI mixture. For this reason, all future pilot plant batches were to be run in Hastelloy C reactors fitted with Hastelloy C heat exchangers. This construction material was found to be compatible with all components of the reaction under the conditions employed.

A second problem discovered with the pilot scale reaction was caused by the inefficient removal of hydrogen chloride gas from the reaction mixture. In contrast to the typical laboratory setup, the reaction was run with very little head space in the reactor, with only a gentle reflux of toluene, and with only moderate agitation. The rearrangement of carbamate **14** to isocyanate **13** is driven by the loss of hydrogen chloride from the system. If this does not occur effectively, then significant concentrations of **13** and **14** as well as **12** and CSI could exist in solution at any one time, and their combination could result in the formation of impurities. This effect was discovered when a number of reactions were conducted in sealed tubes from which, of course, no hydrogen chloride could escape. Upon workup of these reactions, crude material of quality practically identical to that produced in the pilot plant was obtained. It was therefore decided that, in future pilot plant runs, a much larger head space would be utilized together with a much more vigorous toluene reflux and rapid agitation.

When the above equipment and processing modifications were implemented in two subsequent reactions run on a 24 kg scale of 2,6-diisopropylphenol, the process behaved much as had been observed on a laboratory scale. The yields from the pilot plant were 22.6 and 23.6 kg (65% and 68% yields, respectively) of excellent quality sulfamate **3**.

One area for improvement in any subsequent process development work was obviously an increase in the moderate 65−72% overall yield. Since the crude yields of **3** after precipitation from water were relatively high, at around 95%, it appeared that the major yield loss was occurring during

(13) Hedaytullah, M.; Hugueny, J. C. *Phosphorus Sulfur Relat. Elem.* **1984**, *19*, 167.
(14) (a) Lohaus, G. *Chem. Ber.* **1972**, *105*, 2791. (b) Lattrell, R.; Lohaus, G. *Chem. Ber.* **1972**, *105*, 2800.

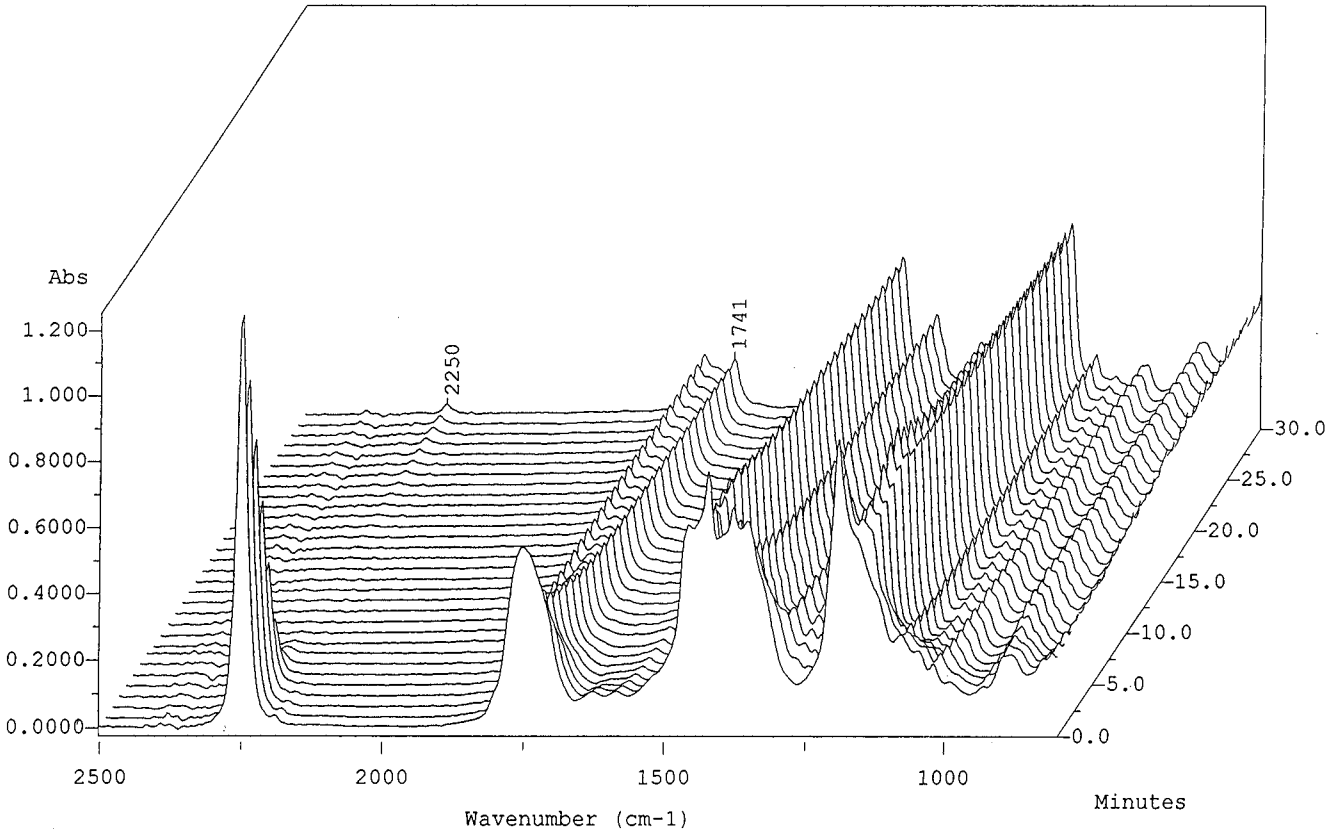


Figure 2. **In-process IR spectra for the formation of carbamate 14 from phenol 12 and CSI.**

the final isopropyl alcohol/hexane recrystallization. A new process for compound **3**, therefore, that used a solvent suitable both for the reaction between phenol **12** and CSI and for the crystallization of **3** would be expected to result in an increase in the chemical yield. Heptane was found to have the desired characteristics. Since the boiling point of the heptane mixture was 12−13 °C lower than that for toluene, a reaction time of at least 30 h was necessary instead of the previous 12−16 h period. This reaction was conveniently followed in the laboratory by making real-time in-process FT IR measurements using Applied System's ReactIR system. For instance, as phenol **12** was added to CSI in heptane at 40 °C, an immediate reduction in the intensity of the isocyanate absorption at 2250 cm^{-1} due to CSI was observed together with a corresponding increase in the intensity of the carbonyl absorption at 1741 cm^{-1} due to formation of carbamate **14** (Figure 2). This trend continued as **12** was effectively titrated against CSI. Then as the mixture was heated to reflux and held at that temperature, the slow conversion of **14** to the product **13** was observed, the latter compound having, amongst others, a characteristic absorption band at 2250 cm^{-1} due to the newly formed isocyanate group (Figure 3). After a period of 30 h at reflux, and with no further increase in intensity of the isocyanate band, it was apparent that the conversion was complete and that the quench process could proceed (Figure 4). Thus, apart from providing valuble process information, the in-process IR measurements also confirmed the reaction mechanism proposed previously.

Following the conversion of phenol **12** to isocyanate **13**, 2.5 equiv of water was added to the hot heptane solution to destroy the slight excess of CSI and to hydrolyze and decarboxylate **13** to sulfamate **3**. The product precipitated from the solution at this point but was redissolved by the addition of a small quantity of THF. In order to remove impurities derived from the hydrolysis of the excess CSI, the hot THF/heptane solution was washed with water. After the final phase separation, the solution was simply cooled to crystallize the product **3**. Therefore, by using heptane as the reaction solvent, a new streamlined process had been developed which eliminated the distillation of solvents prior to the quench, the isolation and drying of the crude product, and the subsequent recrystallization step.

The new process was successfully scaled up to 240 g of 2,6-diisopropylphenol in the laboratory (87−91% yields) and then demonstrated on a pilot scale of 24 kg of the phenol. An overall yield of 86% was obtained, a significant improvement over the yield from the toluene process. The sulfamate **3** was also of excellent quality and met specifications for use in the final coupling reaction to prepare compound **1**.

Development of a Process for the Preparation of CI-1011 (1) from 2,4,6-Triisopropylphenylacetic Acid and 2,6-Diisopropylphenyl Sulfamate. In order to complete the synthesis of CI-1011, acid **2** was converted to the corresponding acid chloride **15** and coupled with sulfamate **3** (Scheme 7). The conversion of acid **2** into acid chloride **15** was first performed on a gram scale using oxalyl chloride as the chlorinating agent with toluene as the solvent and DMF as the catalyst. During the early stages of development of this process, oxalyl chloride was replaced with thionyl chloride, a much cheaper reagent. Again, when DMF was used as the catalyst and toluene as the solvent at 50−60 °C, essentially quantitative conversions of **2** to **15** were achieved. As a safety precaution, the reaction mixture was examined

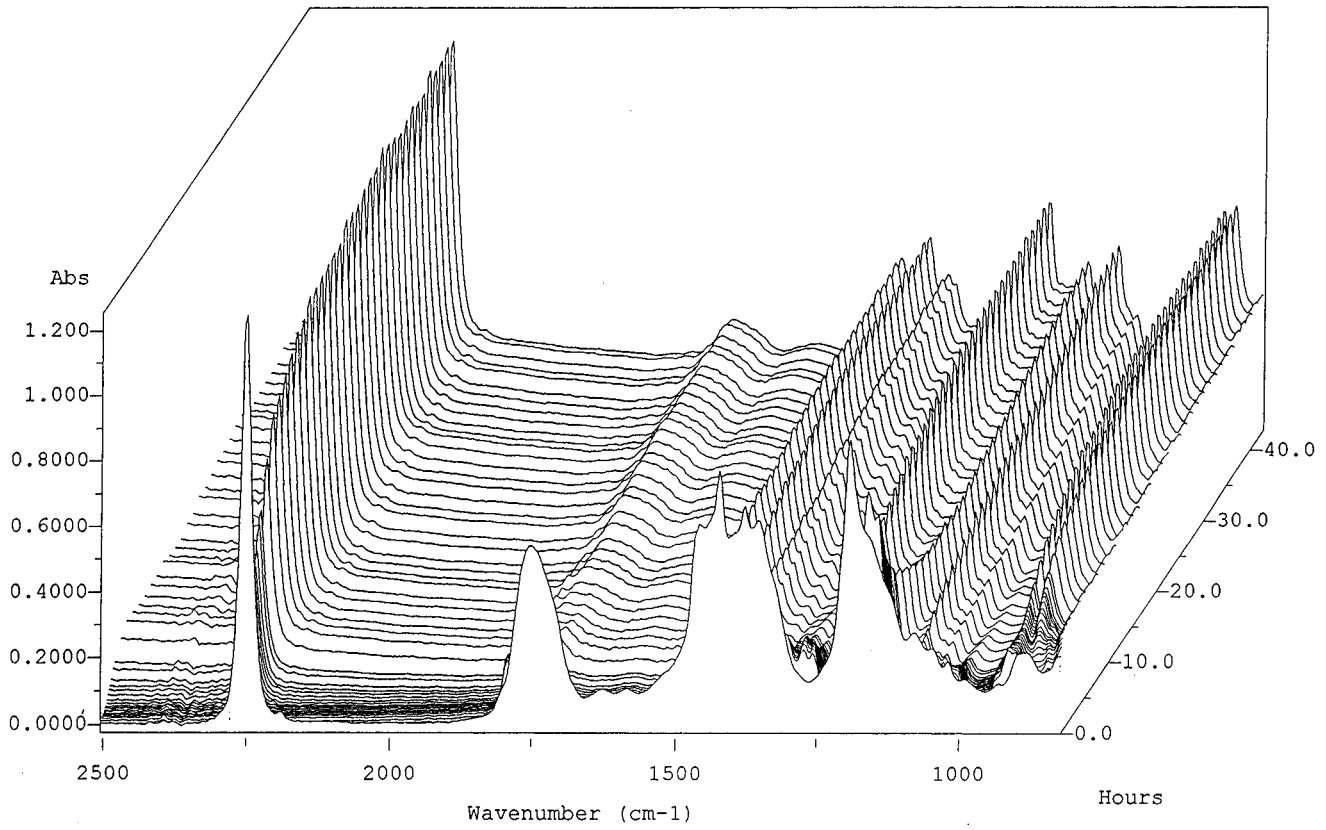


Figure 3. **In-process IR spectra for the formation of isocyanate 14.**

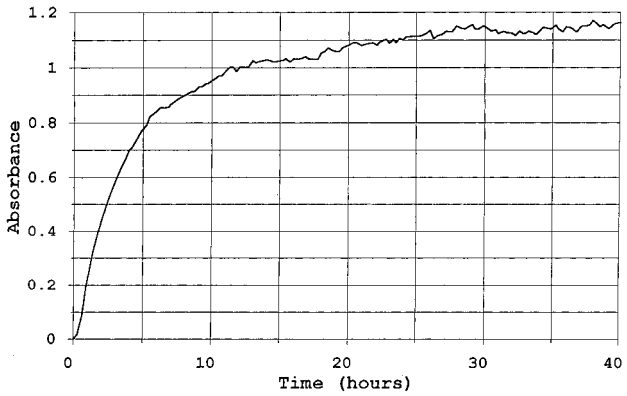
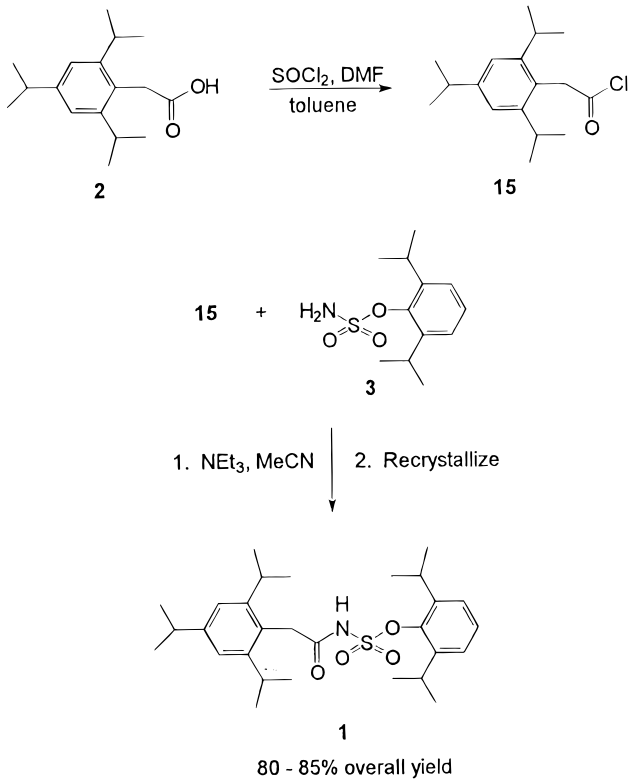


Figure 4. **Increase in intensity of isocyanate IR absorption band at 2250 cm^{-1} due to 14 with time.**

using sealed-cell differential scanning calorimetry due to the runaway hazards associated with the formation of the Vilsmeier reagent. The hazards analysis revealed the absence of any exothermic decompositions up to a temperature of 200 °C, and the process was thus considered safe for demonstration on both a large laboratory scale and a pilot scale.

Originally, the process used 2 equiv of thionyl chloride to attain the desired conversion in a reasonable period of 1−2 h. However, any reduction in the thionyl chloride charge that could be made would reduce the raw material costs and, more significantly, the costs associated with the waste treatment and disposal of excess amounts of this reagent. The effect of the charge of thionyl chloride and the effect of reaction concentration on the rate of conversion of **2** to **15** were demonstrated, again using Applied System's ReactIR apparatus to make in-process FT IR measurements. Following the addition of thionyl chloride to a solution of

Scheme 7. **Preparation of CI-1011 (1) from acid 2 and sulfamate 3**



acid **2** in toluene containing catalytic DMF, both the disappearance of the IR band at 1710 cm^{-1} due to the starting acid and the increase in intensity of the IR band at 1806 cm^{-1} due to the acid chloride were monitored as the solution was heated to 50 °C and held at that temperature (Figure 5).

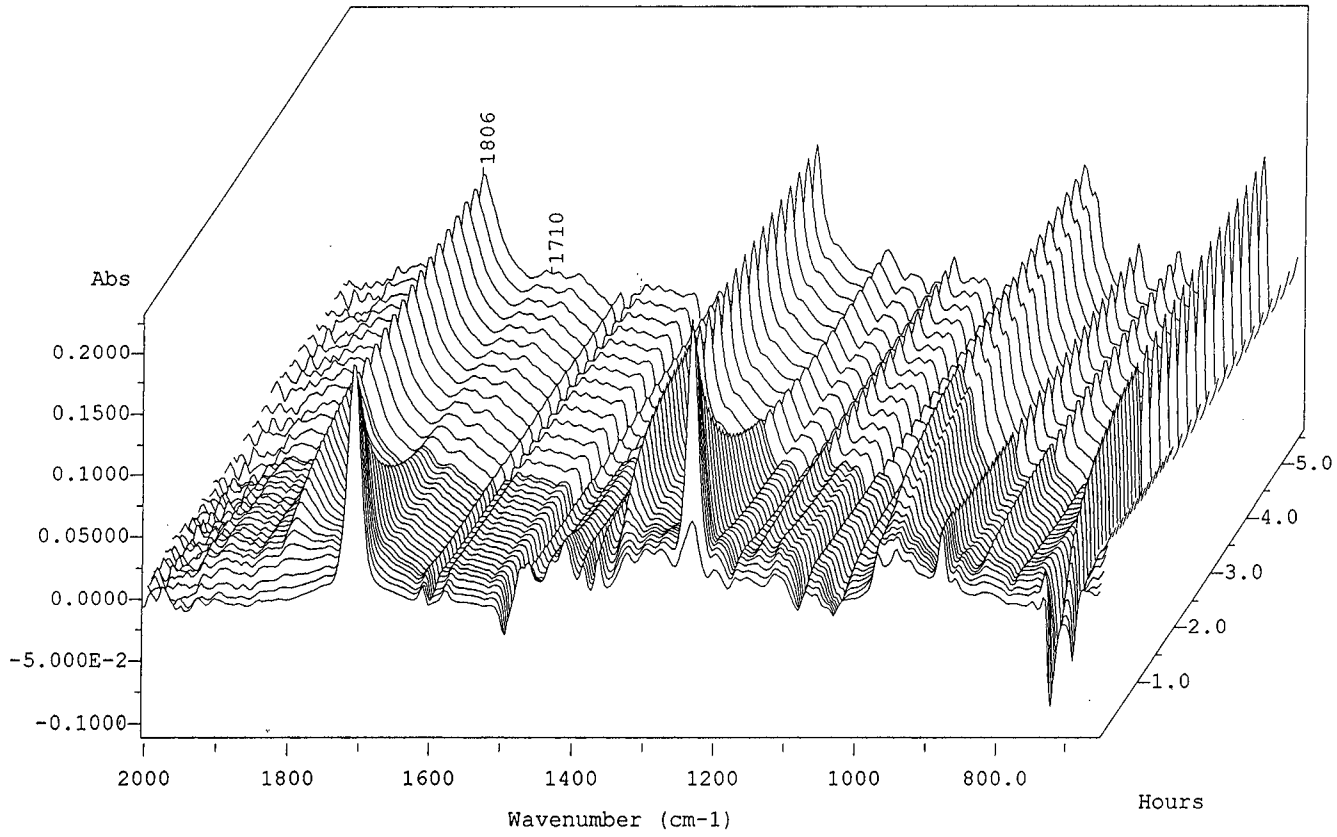


Figure 5. **In-process IR spectra for the formation of acid chloride 15 from acid 2.**

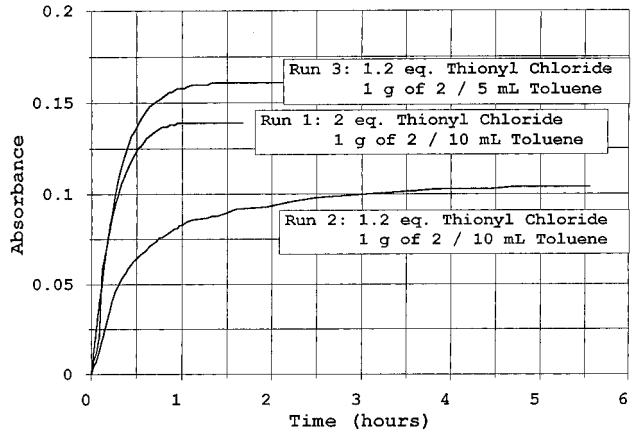


Figure 6. **Effect of the charge of thionyl chloride and reaction concentration on the rate of conversion of 2 to 15 (peak at 1806 cm^{-1}).**

The results indicated that, under the original conditions using 2 equiv of thionyl chloride and a concentration of 1 g of acid **2**/10 mL of toluene, the reaction was complete in 1 h 10 min at 50 °C (run 1). At the same concentration, but using 1.2 equiv of thionyl chloride, a reaction time of 5 h was required to achieve a similar degree of conversion (run 2). However, by doubling of the reaction concentration to 1 g of the starting acid/5 mL of toluene while the lower thionyl chloride stoichiometry was maintained, the reaction time was reduced to 1 h 20 min at 50 °C (run 3). These results are summarized in Figure 6 (note that the magnitude of the final absorbance was dependent on the reaction concentration). The latter reaction conditions were subsequently used in the pilot plant demonstration of the process to prepare intermediate **15** from **2**.

Finally, optimum conditions for the coupling reaction between acid chloride **15** and sulfamate **3** and the isolation and purification of the final pharmaceutical product **1** were determined. Toluene and excess thionyl chloride were removed from the solution of **15** by vacuum distillation and replaced with acetonitrile. Acetonitrile was chosen as the solvent for the coupling reaction because, apart from producing superior yields, it offered a practical advantage in that it gave a highly crystalline and readily filterable crude product when the reaction mixture was quenched into aqueous hydrochloric acid. This was not the case when THF was used as the solvent. As the solvent for the acid chloride forming step, toluene was also examined as the solvent for the coupling reaction. Although it did simplify the process by avoiding the solvent displacement operation, the reaction in toluene resulted in significantly lower yields than those achieved in the process using acetonitrile.

The solution of acid chloride **15** was added to an acetonitrile solution of sulfamate **3** (1 equiv) and triethylamine while the temperature was maintained at 0−10 °C. It was found that at least 2 equiv of triethylamine was necessary to maximize the yield of the final product since CI-1011 (**1**) itself forms a salt with triethylamine. The reaction mixture was quenched into aqueous hydrochloric acid and the crude product isolated. Generally, the crude material was dried before recrystallization from hot isopropyl alcohol; however, laboratory studies did indicate that the solvent-wet product could be recrystallized directly, albeit with a slightly lower throughput, without any detrimental effect on the quality or the yield of the final product. Isopropyl alcohol was by far the most effective purification solvent for CI-1011. Crude product of variable quality was consistently upgraded to give

CI-1011 that met specifications for pharmaceutical use with material recoveries of approximately 90%. The complete process was run as described up to a 560 g scale of **2** in the laboratory and was successfully translated to the pilot plant to produce 57 kg (85% yield) and 53 kg (81% yield) milled lots of CI-1011 that met all specifications for clinical use. Additional laboratory work confirmed the robustness of the process. Separate experiments in which the starting materials **2** and **3** were individually overcharged by 10%, in which the solvent volumes were all reduced by 25%, and in which the temperature of the mixture during the addition of **15** to **3** was allowed to exotherm to 41 °C all gave acceptable final product after recrystallization, in the standard 80−85% yield range.

In summary, we have successfully developed and demonstrated a scalable synthetic process to manufacture the ACAT inhibitor, CI-1011 (**1**). On the basis of the pilot scale experience acquired to date, we expect the process to be scalable to produce even larger batch sizes of CI-1011.

Experimental Section

General Methods. All reagents, solvents, and processing aids are commercial products and were used as received. All reactions were performed under a nitrogen atmosphere. Due to the possibility of bis(chloromethyl) ether formation, the chloromethylation reaction to form **8** was carried out in a well-ventilated fume hood and all equipment was washed with dilute base after use. For reactions run on a pilot scale, glass-lined reactors having variable rate agitation, a −10 to 140 °C jacket temperature range, and a 60 mmHg vacuum to at least a 30 psig pressure rating were used, unless otherwise stated. All equipment was inspected visually for cleanliness and integrity before use. Nitrogen was routinely used to break vacuums and to blanket reactions for safety reasons. Standard equipment cleaning procedures were followed.

Melting points were measured on a Mettler FP80 apparatus and are uncorrected. The following conditions were used for vapor phase chromatography (VPC): DB-05, 15 m × 0.25 mm i.d. column; 50 °C (hold 5 min) to 280 °C (hold 5 min) at 15 °C/min temperature program; 150 °C injector temperature; 300 °C detector temperature; 1.0 μL injector volume. The following conditions were used for high-performance liquid chromatography (HPLC): YMC ODS-AQ, 3 μm, 150 × 4.6 mm column; 550 mL of tetrahydrofuran/450 mL of water/250 μL of phosphoric acid mobile phase; 0.8 mL/min flow rate; 20 μL injection volume; detection at 214 nm. Proton NMR spectra were recorded at 200 MHz on a Varian Gemini-200 spectrometer using tetramethylsilane as an internal standard. IR spectra were measured on an Analect Diamond-20 spectrometer, and the IR absorption bands reported have either strong or very strong intensities. Elemental analyses were performed on a CEC 440 elemental analyser.

2,4,6-Triisopropylbenzyl Alcohol (5). To a rapidly stirred slurry of lithium aluminum hydride (80 g, 2.11 mol) in diethyl ether (3 L) was added a solution of 2,4,6-triisopropylbenzoyl chloride (400 g, 1.50 mol) in diethyl ether (1.8 L) over 1 h while the batch temperature was maintained at 24−28 °C (ice bath required). The reaction mixture was stirred at 23−26 °C for 4 h and then quenched by the addition of a saturated sodium sulfate solution (5 L). The first 150 mL of the aqueous solution was added dropwise over 30 min with ice bath cooling in order to control foaming; the remainder of the aqueous solution was added more rapidly over 20 min. The biphasic mixture was stirred at ambient temperature for 1 h, and the lower aqueous layer was separated and extracted with diethyl ether (1.2 L). The combined diethyl ether extracts were washed with water (1.4 L), dried over anhydrous magnesium sulfate (500 g), and filtered. The solution was concentrated under vacuum, and the resulting solid was dried in a vacuum oven at 40 °C to give crude **5** (342.6 g, 98%) as a white solid: VPC (by area) 100%. The crude product was dissolved in ethyl alcohol (1 L) at 60 °C, and to the stirred solution was added water (560 mL). The solution was cooled to 5−10 °C and stirred for a further 3 h. The resulting slurry was filtered, and the filter cake was washed with 1:1 ethyl alcohol/water (300 mL) and dried in a vacuum oven at 55 °C to give **5** (310.5 g, 88%) as white needles: mp 94−95 °C; VPC (by area) 100%; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 2H), 4.76 (s, 2H), 3.37 (septet, J = 7 Hz, 2H), 2.88 (septet, J = 7 Hz, 1H), 1.27 (d, J = 7 Hz, 12H), 1.25 (d, J = 7 Hz, 6H); IR (1% KBr disk) 3246, 2962, 1606, 1458, 1009 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.62; H, 10.98.

2,4,6-Triisopropylbenzyl Chloride (8) by the Chlorination of 5. To a stirred solution of **5** (388.5 g, 1.66 mol) in toluene (1.8 L) warmed to 40 °C was added a solution of thionyl chloride (276 g, 2.32 mol) in toluene (900 mL) over 1 h 20 min while the batch temperature was maintained at 40−48 °C. The reaction mixture was heated to 70 °C and stirred for 2.5 h at 70−73 °C. Toluene and excess thionyl chloride were removed under vacuum, and the resulting brown oil was vacuum distilled at 5−10 mmHg. A major fraction was collected at a vapor temperature of 135−140 °C to give **8** (410.7 g, 98%) as a clear, colorless oil that crystallized upon standing: VPC (by area) 99.9%. The product was identical spectroscopically to that prepared by the chloromethylation of 1,3,5-triisopropylbenzene described below.

2,4,6-Triisopropylbenzyl Cyanide (7). To a stirred slurry of sodium cyanide (223 g, 4.55 mol) in DMSO (980 mL) heated to 90 °C was added premelted (40 °C) **8** (677 g, 2.68 mol) in four equal portions over 30 min. The addition of **8** was accompanied by an exotherm which raised the temperature of the reaction mixture to 135 °C. The mixture was cooled to 100 °C and stirred for 1 h, and then it was cooled to 70 °C and poured into rapidly stirred water (2.8 L). The resulting slurry was stirred at ambient temperature for 3 h and filtered. The filter cake was washed with water (3 L) and dried in a vacuum oven at 50 °C to give crude **7** (668 g) as a light brown solid. The crude product was dissolved in boiling hexane (1 L), and the solution was filtered, the filter paper being rinsed with hot hexane (200 mL). After the filtrates were cooled to 5−10 °C, the resulting slurry was filtered, and the filter cake was washed with cold hexane (2 × 300 mL) and dried in a vacuum oven at 50 °C to give **7** (525.9 g, 81%) as off-white needles: mp 86.9−87.4 °C (lit.[5] mp 89−90 °C); VPC (by area) 99.5%; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 2H), 3.73 (s, 2H), 3.15 (septet,

J = 7 Hz, 2H), 2.88 (septet, J = 7 Hz, 1H), 1.29 (d, J = 7 Hz, 12H), 1.25 (d, J = 7 Hz, 6H); IR (1% KBr disk) 2968, 2243, 1608, 1577, 1469, 1387, 1363 cm^{-1}.

2,4,6-Triisopropylphenylacetic Acid (2) by the Hydrolysis of 7. A stirred mixture containing **7** (524.8 g, 2.16 mol), potassium hydroxide (776 g, 13.83 mol), diethylene glycol (3.9 L), and water (156 mL) was heated under reflux (140−160 °C) for 16.5 h. The resulting solution was cooled to 70 °C and poured into rapidly stirred water (8 L). Hydrochloric acid (37%, 1275 mL) was added to the mixture to give a slurry, which was stirred at ambient temperature for 1.5 h, cooled to 8 °C, filtered, and washed with water (11 L). The product was dried in a vacuum oven at 50−60 °C to give crude **2** (562.3 g, 99%) as a white powder. The crude product was dissolved in ethyl alcohol (2520 mL), warmed to 45 °C, and filtered. To the stirred solution was added water (2315 mL) over 45 min while the batch temperature was maintained at 40−45 °C. The resulting slurry was stirred for 30 min at 40 °C, cooled to 6 °C and stirred for 2 h, and filtered. The filter cake was washed with 1:1 ethyl alcohol/water and dried in a vacuum oven at 50 °C to give **2** (513.3 g, 91%) as white needles: mp 144.7−145.5 °C (lit.[5] mp 148−149 °C); HPLC (by area) 99.7%; ^{1}H NMR (DMSO) δ 12.29 (br s, 1H), 6.88 (s, 2H), 3.66 (s, 2H), 3.10 (septet, J = 7 Hz, 2H), 2.85 (septet, J = 7 Hz, 1H), 1.21 (d, J = 7 Hz, 6H), 1.17 (d, J = 7 Hz, 12H); IR (1% KBr disk) 2962, 1705, 1236 cm^{-1}.

2,4,6-Triisopropylbenzyl Chloride (8) by the Chloromethylation of 1,3,5-Triisopropylbenzene. A stirred mixture of 1,3,5-triisopropylbenzene (700 g, 3.43 mol), paraformaldehyde (180 g, 6.0 mol), hydrochloric acid (37%, 2.61 L), and acetic acid (1.17 L) was heated to 40 °C. Anhydrous hydrogen chloride gas (120 g) was added to the mixture over 1.5 h, the batch temperature was raised to 75 °C, and the mixture was stirred for 16 h. A second charge of anhydrous hydrogen chloride gas (45 g) was made over 40 min, and the mixture was stirred at 75 °C for an additional 3 days. The reaction mixture was cooled to ambient temperature, and the lower aqueous acetic acid layer was separated. The upper product oil was washed with water (300 mL), at 40 °C to prevent crystallization of the product, and then was vacuum distilled at 1 mmHg, to give fractions that were collected over a 118−120 °C vapor temperature range and at a batch temperature of 130 °C. An early fraction of 61.8 g contained 2.3% of unreacted 1,3,5-triisopropylbenzene. The major higher boiling fraction was collected to give **8** (752 g, 87%) as a clear, colorless oil, which crystallized upon standing: mp 33.2−33.7 °C (lit.[15] mp 32−34 °C); VPC (by area) 99.8%; ^{1}H NMR ($CDCl_3$) δ 7.03 (s, 2H), 4.76 (s, 2H), 3.32 (septet, J = 7 Hz, 2H), 2.89 (septet, J = 7 Hz, 1H), 1.30 (d, J = 7 Hz, 12H), 1.26 (d, J = 7 Hz, 6H); IR (1% KBr disk) 2962, 1608, 1460, 1385, 1363, 1259, 879 cm^{-1}.

2,4,6-Triisopropylphenylacetic Acid (2) on Pilot Scale by the Cyanation and Hydrolysis of 8. To a reactor were charged **8** (40 kg, 158.2 mol), sodium cyanide (8.1 kg, 165.3 mol), tetra-*n*-butylammonium bromide (0.6 kg, 1.9 mol), toluene (40 L), and water (20 L). With rapid agitation, the mixture was heated to 60−70 °C. External heating was stopped, and the exotherm produced by the reaction was allowed to raise the batch temperature to 80−85 °C. If the temperature exceeded this range, it could be controlled by external cooling or by reducing the rate of agitation. After heating at 80−85 °C for 7 h, water (10 L) was added and the mixture cooled to 35−40 °C. The lower aqueous phase was separated, and the upper toluene solution was washed with water (3 × 10 L). The combined aqueous washings were treated with aqueous sodium hydroxide to destroy excess sodium cyanide. Propylene glycol (165.8 kg) was added to the toluene solution, and using a vacuum of 30 mmHg, toluene was distilled out of the mixture to a final batch temperature of 70 °C. The propylene glycol solution was transferred to a stainless steel reactor, and sodium hydroxide (29.7 kg, 742.5 mol) and water (18.5 L) were added. With agitation, the mixture was heated at 130−135 °C for 19 h. After cooling to 60 °C, the reaction mixture was transferred to a reactor containing stirred water (210 L). The hydrolysis reactor was rinsed with water (2 × 50 L), and the rinses were added to the quenched mixture. Hydrochloric acid (37%, 80.4 kg) was added to the cooled aqueous solution (5−10 °C), and the resulting slurry was stirred at 5−10 °C for 3 h and filtered. The filter cake was washed with water (150 L) and dried in a vacuum oven at 50−55 °C to give crude **2** (42 kg) as a light brown solid. To a reactor were charged the crude product, activated carbon (6 kg), Celite (2 kg), and methyl alcohol (90 L). The slurry was stirred at ambient temperature for 21.5 h and filtered. The filter cake was washed with methyl alcohol (30 L), and to the combined filtrates, with agitation, was added water (160 L). The resulting slurry was stirred at ambient temperature for 6.5 h, cooled to 5−10 °C, and filtered. The filter cake was washed with water (150 L) and dried in a vacuum oven at 50−55 °C to give **2** (36.8 kg, 89%) as an off-white powder: mp 141.5−142.6 °C (lit.[5] mp 148−149 °C); HPLC (by area) 99.1%. The product was identical spectroscopically to that prepared by the hydrolysis of **7** described above.

2,4,6-Triisopropylphenylacetic Acid (2) by the Hydroxyalkylation and Reduction of 1,3,5-Triisopropylbenzene. From a stirred solution of 50% aqueous glyoxylic acid (87.6 g, 0.59 mol) in acetic acid (700 mL) was distilled 375 mL of an acetic acid/water mixture at atmospheric pressure. To the cooled glyoxylic acid solution were added 1,3,5-triisopropylbenzene (50 g, 0.25 mol), 97% sulfuric acid (24 g, 0.25 mol), and acetic acid (75 mL). The resulting mixture was heated under reflux at 116 °C for 19 h, cooled to ambient temperature, and transferred to a glass pressure reactor. Aqueous hydriodic acid (47%, 133.1 g, 0.49 mol) and acetic acid (50 mL) were added, and the stirred mixture was heated at 105 °C in a sealed system for 15 h. The maximum pressure developed was 8 psig. After cooling to ambient temperature, the mixture was poured into a rapidly stirred solution of sodium metabisulfite (25 g, 0.13 mol) in water (2 L), and the aqueous solution was extracted with toluene (2 × 490 mL). The combined toluene extracts were washed with water (245 mL) and treated with activated carbon (6.1 g) for 3 h. The slurry was filtered, and 10% aqueous sodium hydroxide (200 mL) was added to the filtrates to give a mixture consisting of three phases. The middle phase was

(15) Barclay, L. R. C.; Sonawane, H. R.; Hudson, J. C. *Can. J. Chem.* **1972**, *50*, 2318.

separated, washed with toluene (100 mL), and diluted with water (490 mL). The aqueous solution was acidified to pH 9 with 10% aqueous hydrochloric acid (22 mL), filtered, and then acidified to pH 3 with additional 10% aqueous hydrochloric acid (75 mL). The resulting slurry was cooled to 10 °C and filtered. The filter cake was washed with water (100 mL) and dried in a vacuum oven at 50 °C to give crude **2** (50.9 g) as a light brown solid. To the crude product were added activated carbon (5 g) and methyl alcohol (120 mL). The slurry was stirred at ambient temperature for 1 h and filtered. The filter cake was washed with methyl alcohol (130 mL), and to the combined filtrates at 55 °C was added water (90 mL). The resulting slurry was cooled to 5−10 °C and filtered. The filter cake was washed with cold 1:4 methyl alcohol/water (75 mL) and dried in a vacuum oven at 50 °C to give **2** (43.7 g, 68%) as an off-white powder: mp 137−145 °C (lit.[5] mp 148−149 °C); HPLC (by area) 97.9%. The product was identical spectroscopically to that prepared by the hydrolysis of **7** described above.

2,6-Diisopropylphenyl Sulfamate (3) on Pilot Scale Using Toluene as the Reaction Solvent. To a Hastelloy C reactor were charged 2,6-diisopropylphenol (24 kg, 134.6 mol) and toluene (120 L), and to this agitated solution at ambient temperature was added a solution of chlorosulfonyl isocyanate (20 kg, 141.3 mol) in toluene (80 L). The exotherm produced by the reaction caused the batch temperature to rise to 35 °C. With rapid agitation, the mixture was heated under reflux (91−106 °C) for 14 h and then cooled to ambient temperature. Toluene was distilled out of the mixture under a vacuum of approximately 1 mmHg and to a final batch temperature of 60 °C. The resulting oil was transferred over a period of 20 min to a reactor containing rapidly agitated water (400 L). The Hastelloy C reactor was rinsed with acetonitrile (7 kg) and then water (50 L), and the rinses were transferred to the agitated aqueous mixture. The resulting slurry was stirred at ambient temperature for 16 h and at 10−15 °C for 2 h, and then it was filtered. The filter cake was washed with water (2 × 60 L) and dried in a vacuum oven at 45−50 °C to give crude **3** (33.3 kg) as a light brown solid. To a reactor were charged the crude product, isopropyl alcohol (11 L), and hexane (122 L). The mixture was heated to 60 °C to dissolve all the solids and was then cooled to 25 °C over 6 h to crystallize the product. The slurry was stirred at 20−25 °C for 12 h and at 0−5 °C for 2.5 h, and then it was filtered. The filter cake was washed with hexane (60 L) and dried in a vacuum oven at 45−50 °C to give **3** (23.6 kg, 68%) as white plates: mp 111.2−112.1 °C (lit.[13] mp 114 °C); HPLC (by area) 100%; ^{1}H NMR ($CDCl_3$) δ 7.1−7.3 (m, 3H), 5.16 (br s, 2H), 3.44 (septet, J = 7 Hz, 2H), 1.23 (d, J = 7 Hz, 12H); IR (1% KBr disk) 3385, 3282, 2960, 1564, 1468, 1444, 1373, 1362, 1190 cm^{-1}.

2,6-Diisopropylphenyl Sulfamate (3) on Pilot Scale Using Heptane as the Reaction Solvent. To a Hastelloy C reactor were charged chlorosulfonyl isocyanate (19.1 kg, 135 mol) and heptane (92 kg), and to this agitated solution at ambient temperature was added 2,6-diisopropylphenol (24 kg, 134.6 mol). The exotherm produced by the reaction caused the batch temperature to rise to 51 °C. With rapid agitation, the mixture was heated under reflux (83−95 °C) for 40 h and then cooled to 68−75 °C. Water (6 L) was added slowly to the mixture, at such a rate as to control the degree of foaming, followed by THF (4 L) to dissolve the precipitated solids. A second charge of water (30 L) was made to the solution, again at such a rate as to control the degree of foaming. The biphasic mixture was agitated rapidly at 68−75 °C for 1 h and allowed to settle. The lower aqueous phase was separated, and the upper heptane layer was washed with more water (2 × 18 L) at 68−75 °C and then cooled to ambient temperature at approximately 1 °C/min to crystallize the product. The slurry was cooled to 5−10 °C and stirred for 3 h, and then it was filtered. The filter cake was washed with heptane (40 kg) and dried in a vacuum oven at 50−55 °C to give **3** (29.9 kg, 86%) as white plates: mp 108.5−110.5 °C (lit.[13] mp 114 °C); HPLC (by area) 99.7%. The product was identical spectroscopically to that prepared using toluene as the reaction solvent described above.

2,6-Diisopropylphenyl [(2,4,6-Triisopropylphenyl)-acetyl]sulfamate (1) on Pilot Scale. To a reactor containing an agitated solution of **2** (33.9 kg, 129.2 mol) and dimethylformamide (40 g, 0.55 mol) in toluene (100 L) warmed to 50−60 °C was added a solution of thionyl chloride (18.5 kg, 155.5 mol) in toluene (70 L). The solution was added over 25 min while the batch temperature was maintained at 50−60 °C. The resulting mixture was heated at 50−55 °C for 5.5 h and cooled to ambient temperature. Toluene and excess thionyl chloride were vacuum distilled out of the reaction mixture to a maximum batch temperature of 75 °C. The residual oil was cooled to ambient temperature, dissolved in acetonitrile (106 kg) and cooled to 5−10 °C, and then added to a 0−5 °C solution of **3** (33.3 kg, 129.4 mol) and triethylamine (32.7 kg, 323 mol) in acetonitrile (103 kg). The solution was added at such a rate as to maintain the batch temperature at 0−10 °C. The reaction mixture was stirred at 0−10 °C for 3 h and at ambient temperature for 16.5 h, and then it was transferred into a rapidly agitated solution of hydrochloric acid (37%, 23.6 kg) and isopropyl alcohol (109 L) in water (602 L) while the batch temperature was maintained at 20−35 °C. The resulting slurry was cooled to 10−15 °C, stirred for 5 h, and filtered. The filter cake was washed with water (160 L) and dried in a vacuum oven at 50−55 °C to give crude **1** (63.3 kg) as a light brown solid. To a reactor were charged the crude product and isopropyl alcohol (601 L). The mixture was heated to reflux (78−83 °C) to dissolve all the solids and filtered. The filtration equipment was rinsed with isopropyl alcohol (35 L), and the combined filtrates were cooled to ambient temperature over 2 h. The resulting slurry was stirred for a further 2.5 h, cooled to 0−5 °C and stirred for 2 h, and then filtered. The filter cake was washed with cold isopropyl alcohol (115 L), dried in a vacuum oven at 50−55 °C, and milled to give **1** (52.6 kg, 81%) as a white powder: mp 169.5−170.4 °C; HPLC (w/w *vs* reference standard) 99.1%; ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, 1H), 7.30−7.05 (m, 5H), 3.96 (s, 2H), 3.43 (septet, J = 7 Hz, 2H), 3.05−2.91 (m, 3H), 1.28 (d, J = 7 Hz, 6H), 1.26 (d, J = 7 Hz, 12H), 1.19 (d, J = 7 Hz, 12H); IR (1% KBr disk) 3446, 3271, 2964, 1738, 1716, 1444 cm^{-1}. Anal. Calcd for $C_{29}H_{43}NO_4S$: C, 69.42; H, 8.64; N, 2.79. Found: C, 69.63; H, 8.59; N, 2.69.

Acknowledgment

We wish to thank Mr. David L. Wehrmeyer for his many practical contributions during the laboratory development and pilot scale demonstration of the process. We also thank Dr. James G. Davidson for helpful suggestions and comments and Mr. Frank Mauro for performing the process-related hazards analysis. We gratefully acknowledge the analytical support provided by Ms. Jana Deering and Ms. Linda D. Shaul.

Received for review September 21, 1996.[⊗]

OP9600419

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