Organic Process Research & Development **1997**, *1,* 211–216

Process Development for the Preparation of a Monopril Intermediate by a Trimethylsilyl-Modified Arbuzov Reaction

Neal G. Anderson,*,† Barbara M. Ciaramella,† Alan F. Feldman,† David A. Lust,† Jerome L. Moniot,† Linda Moran,‡ Robert E. Polomski,† and Steven S. Y. Wang†

Chemical Process Engineering and Chemical Process Technology, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903, and Chemical Development, Bristol-Myers Squibb Company, Swords, Ireland

Abstract:

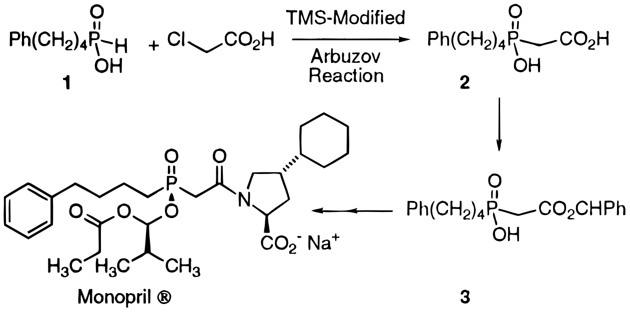
A safe, rugged process for the manufacture of a Monopril intermediate using a trimethylsilyl-mediated Arbuzov reaction was developed. The problems encountered and overcome in iterations from pilot plant to manufacturing are described. The final process gives high-quality product (99.9% purity) in 82% yield. One key was developing an addition sequence to allow for the safe control of the reaction exotherm, complicated by the reflux temperature which decreased with conversion of reagents. Quantitative assessment of the reaction boiling point and exotherm led to the selection of the best addition and heating protocol. The output quality was assured by development of a thermally controlled process that crystallized the product without passing through an intermediate oil dispersion. Alternative conditions for safe control of the exotherm are suggested. Routine safety testing is demonstrated to be critical for rapid development of a safe, optimized process.

An early intermediate in the preparation of Monopril[1] is the phosphinic acid **2**, which can be readily prepared by silicon-modified Arbuzov reactions of phosphonous acids.[2,3] In this paper we detail the development necessary to convert this chemistry into a rugged process for the manufacture of **2** (Scheme 1).

Initial conditions[2] described for the preparation of **2** included using α-bromo esters or acids, trimethylsilyl chloride (TMSCl) and Et_3N, and chloroform (Scheme 2). For development the α-chloro esters and acids were preferred, as they were less expensive. A nonhalogenated solvent was needed to substitute for chloroform. Isolating **2** was a concern, due to the high water solubility reported.[2]

High throughput and low cost were primary driving factors for developing a process to manufacture **2**. For flexibility a relatively high boiling solvent was desirable, as many Arbuzov reactions are run at temperatures above 80 °C.[4] Phosphonium intermediates have been implicated in the Arbuzov reaction,[4] and it was reasoned that a polar solvent would solvate the reactive intermediate and facilitate the reaction.[5] Acetonitrile was selected for process development.[6] The reaction could readily be run under concentrated conditions (1 L of acetonitrile/kg of **1**,[7] reaction concentration of about 1 M after addition of other components). TMSCl and hexamethyldisilazane (HMDS) were selected over the more expensive combination of 1:1 TMSCl/triethylamine.[2] A 1:1 mixture of TMSCl and HMDS was found to be optimal.[8] Upon quenching with water the trimethylsilyl groups are readily hydrolyzed, producing hexamethyldisiloxane. The latter could be removed by phase separation and potentially could be recycled. We found that **2** could be readily crystallized from water (the environmentally friendly solvent), isolated by filtration, and dried.

Scheme 1. **Preparation of Monopril**



Process A. The first iteration of this process used ethyl chloroacetate and the phosphinic acid **1** (Scheme 3). Hydrolysis of the intermediate ethyl ester proved problematic on a multikilogram scale, as a thick layer of solids formed on top of the reaction, and it was necessary to manually force this material into the reaction mixture. In addition, nitrilotriacetic acid was generated during NaOH hydrolysis, and this impurity was carried through into the following step, decreasing the purity of the subsequent intermediate (Scheme 4). Since crystallization of **2** from water proceeded through an oil dispersion to a crystalline suspension, impurities were entrapped with the product in the residual oil. In routine washing operations it was difficult to displace residual oil from the product cake. [Note: Isolations were carried out on a polypropylene filter press, because of the highly

---

† Chemical Process Engineering and Chemical Process Technology.

‡ Chemical Development.

(1) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148.

(2) Thottathil, J. K.; Przybyla, C. A.; Moniot, J. L. *Tetrahedron Lett.* **1984**, *25*, 4737.

(3) Thottathil, J. K. In *Handbook of Organophosphorous Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; pp 63−67.

(4) Engel, R. *The Synthesis of Carbon-Phosphorus Bonds*; CRC Press, Inc.: Boca Raton, FL, 1988; pp 21−38.

(5) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH Verlagsgesellschaft mbH: Weinham, Germany, 1988; pp 126−127.

(6) After initial successful runs in acetonitrile, toluene was also found to be a suitable solvent. Due to time constraints this solvent was not thoroughly investigated.

(7) Compound **1** was prepared from 4-phenyl-1-butene and hypophosphorous acid; cf.: Nifantev, E. E.; Magdeva, R. K.; Shehepeteva, N. P. *J. Gen. Chem. (USSR)* **1976**, *50*, 10124. Nifantev, E. E.; Koroteev, M. P. *J. Gen. Chem. (USSR)* **1966**, *37*, 1366.

(8) Pierce, A. E. *Silylation of Organic Compounds*; Pierce Chemical Co.: Rockford, IL, 1968; pp 19−21.

S1083-6160(97)00202-8 CCC: $14.00

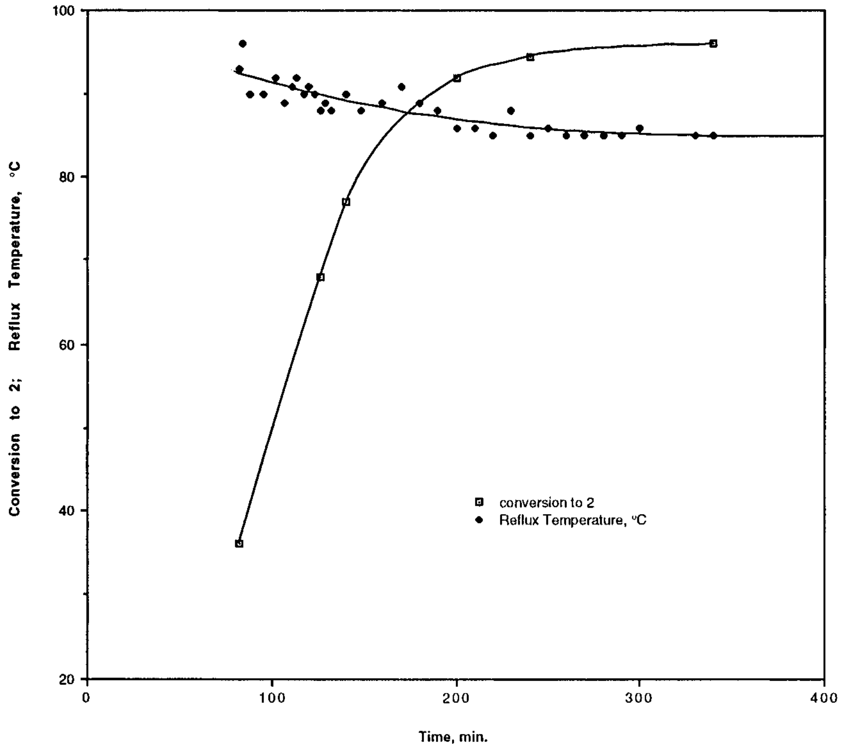
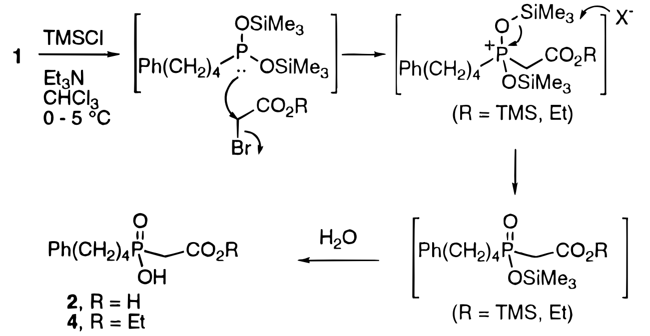
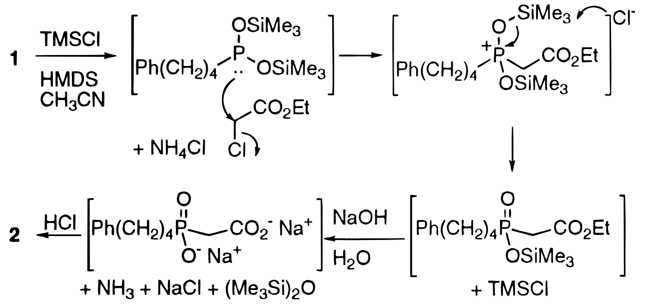


Figure 1. **Decreasing reflux temperature with conversion of 1 to 2, as area % of 2 relative to total area counts. The hydrolysis of bis-silylated 2 is assumed to be instantaneous in the reverse-phase HPLC eluent.**

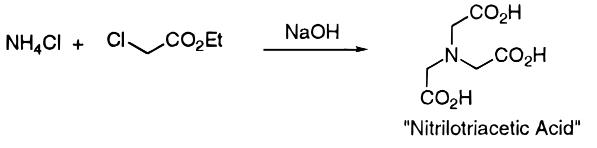
Scheme 2. **Original preparation of 2**



Scheme 3. **Process A**



Scheme 4. **Formation of nitrilotriacetic acid**



Scheme 5. **Processes B, C, D, and E**

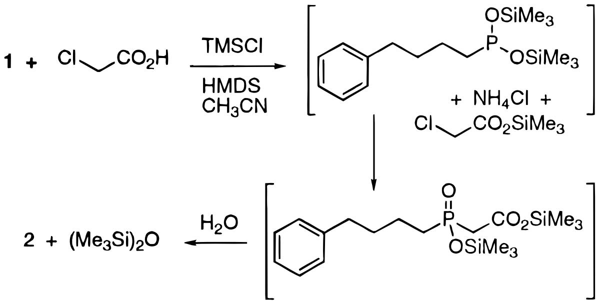


Table 1. **Variations in processes B−E**

process	process variant before heating to reflux	init reflux temp,[a] °C
B	silanes added to **1** and chloroacetic acid at −10 °C	95−100[b]
C	**1**, chloroacetic acid, and TMSCl at 25 °C; HMDS added at 60−70 °C	71
D	**1** and chloroacetic acid combined and added to silanes at 25 °C	75
E	chloroacetic acid added to silanes, then **1** added at 50−55 °C; held at 50−55 °C until at least 50% conversion	75

[a] Equimolar mixture of HMDS and TMSCl found to boil at 81 °C. [b] Dependent on the rate of heating.

corrosive nature of the filtrate (pH <2). Centrifugation and washing may have removed the residual oil more effectively.] Testing showed that esterification of these batches of **2** to **3** was extended by at least 4 h. For suitable conversion, two of three pilot plant batches of **2** were reworked by reslurrying in water.

Process B. To address these problems, ethyl chloroacetate was replaced by chloroacetic acid (process B) (Scheme 5, Table 1). Basic hydrolysis and acidification were not necessary, resulting in a simpler process. Since the reaction was never basic, no nitrilotriacetic acid was formed.

Table 2. **Condensate composition in process B**

reflux temp, °C	condensate composition[a]		
	acetonitrile	TMSCl	HMDS
92	18	12	4
75	18	16	1

[a] Molar ratios determined by ^{1}H NMR.

After quenching with water, hexamethyldisiloxane was removed from the reaction by atmospheric distillation, as the azeotrope with acetonitrile. The resulting oily dispersion of **2** crystallized with cooling, offering no improvement over the process A crystallization in the presence of hexamethyldisiloxane.

To initiate the reaction for process B, HMDS and TMSCl were added to an acetonitrile solution of **1** and chloroacetic acid at −10 °C, and then the reaction mixture was warmed to reflux. No surprises were encountered when the reaction was run on a moderate scale. After heating to about 74 °C at a 130 kg scale, however, the batch temperature quickly rose to afford an initial reflux temperature of about 92 °C, and some of the batch flooded the riser before cooling was applied to the vessel. After reheating, the reflux temperature reached about 75 °C and held constant until completion. Laboratory experiments showed that the reflux temperature decreased as the reaction progressed (see Table 2 and Scheme 5), with consumption of HMDS (bp 126 °C). [Note: TMSCl (bp 57 °C) is consumed during the silylation and then regenerated with the modified Arbuzov condensation.] We recognized that appropriate controls were necessary to prevent the mixture from becoming superheated, releasing large amounts of vapor until the stable boiling point was established.

Process C. Better process control was achieved by adding HMDS as the limiting reagent to a solution of **1**, chloroacetic acid, and TMSCl in acetonitrile at 60−70 °C (process C). The exotherm was controlled by the addition rate of HMDS to the hot reaction; on the basis of our experience with process B, we anticipated that reaction times at this temperature would be convenient for large-scale processing.

Process C performed well upon scale-up in the pilot plant facility, and the process seemed rugged enough for routine production, i.e., the process was reproducible and unexpected processing delays and slight overcharges of reaction components were not anticipated to cause difficulties. The process start-up went very well (Table 3); however, problems were encountered during subsequent manufacturing campaigns. With extended or interrupted HMDS addition in the plant, significant off-gassing resulted, presumably TMSCl and/or HCl escaping when there was an insufficient amount of NH_3 generated from HMDS for neutralization. Incomplete reactions and off-color batches of **2** resulted. When an attempt was made to minimize emissions by conducting the reaction below 65 °C, slow conversions resulted. Furthermore, the overall quality of batches of **2** from process C was poor, producing **3** in average yields of 82%. Reworking of these batches by recrystallization from methyl isobutyl ketone (MIBK) improved the quality and raised yields of **3** to 92%. Process C required further modification to be plantworthy.

Two aspects of the process ruggedness needed to be addressed: devising the best control of reaction exotherms, and improving the routine quality of the isolated product. Recrystallization of **2** from MIBK had been found to raise the output quality, and **2** was found to be readily extracted into MIBK following the quench of the modified Arbuzov reaction. To minimize solvent usage without causing premature crystallization, the first extraction was performed at a slightly elevated temperature (35 °C). Conducting extractions at this temperature raised the solubility of the aqueous phase (and ammonium chloride) in MIBK. Residual ammonium chloride was removed from the combined rich extracts by washing with water until the conductivity levels were low. The rich organic extract was concentrated and residual water removed azeotropically. The warm solution was cooled to about 68 °C and optionally seeded with **2**;[9] for routine operations in manufacturing seeding was not necessary. The suspension was held at this temperature for at least 30 min for good nucleation and the formation of large crystals that would facilitate a rapid filtration. After cooling to 0−5 °C and holding for at least 1 h, the product was isolated by centrifugation and washing with cold MIBK. These conditions led to a reproducible, temperature-controlled crystallization of **2** without oiling. High-quality **2** was produced, with improved yields of the subsequent Monopril intermediate. Use of a stainless steel centrifuge was possible, considering the reduced corrosivity of the filtrates. With a rugged isolation in hand, the addition sequence was addressed again.

Process D. Process D incorporated the above isolation, using another variant of the addition protocol. An acetonitrile solution of **1** and chloroacetic acid was added to a kettle containing TMSCl and HMDS below 25 °C, and the reaction mixture was heated to reflux in stages to gradually increase conversion and avoid superheating. When addition was complete, the reaction mixture was held at 45 °C for about 3 h, to ensure conversion to **2** of at least 40% (an empirically chosen limit). Then the reaction mixture was heated to reflux over 2 h and held at reflux until the reaction was complete. No TMSCl/HCl fumes were given off, and the lowest impurity reaction profile seen to that time was produced.

Process D was examined in the pilot plant, and it handled well. High-quality product was produced in good yield (Table 3). However, since the decreasing surface area to volume ratio of larger tanks used on scale-up decreases the effective area for external cooling, the exotherm posed a potential concern for process control. We sought a fail-safe method for control of larger batches.

We reasoned that by combining TMSCl and HMDS at the start of the reaction and conducting a sizable proportion of the reaction below the boiling point, greater control of the reaction would be possible. By first silylating chloroacetic acid, some of the exotherm could be controlled before charging the valuable intermediate **1**. The subsequent

---

(9) For discussions on crystallization and seeding, cf.: Mullin, J. W. *Crystallization*; CRC Press: Cleveland, OH, 1972. *Handbook of Industrial Crystallization*; Myerson, A. S., Ed.; Butterworth-Heinemann: Boston, MA, 1993.

Table 3. **Performance on scale for processes C−E**

process	scale	no. of batches	input of 1 per batch, kg	total of 2 produced, kg	av yield, %	av purity, %
C	pilot plant (New Brunswick, NJ)	8	9−137	362	85	98
C	manufacturing start-up (Swords, Ireland)	5	232	1250	85	97
D	pilot plant (Swords, Ireland)	3	35	114	85	99
E	pilot plant (New Brunswick, NJ)	2	15 and 110	135	86	99.7
E	manufacturing start-up (Swords, Ireland)	5	275−343	1570	82	99.9

Table 4. **Maximum exotherms in process E reactions**

[**2**] by HPLC at time of analysis, %	max exotherm,[a] °C/min
1.1	10.5
19.7	3.6
41.3	2.6

[a] As determined by Fauske RSST apparatus.

exotherm could be controlled by cooling and moderating the addition rate of **1**. As expected, the longer the reactions progressed at lower temperature, the less heat of reaction was released upon heating to reflux (Table 4). With these features incorporated, process E was developed.

Process E. In Process E, TMSCl and HMDS were first treated with an acetonitrile solution of chloroacetic acid at 25 °C. Then an acetonitrile solution of **1** was added as the rate-limiting step, allowing the reaction mixture to warm to 50−55 °C. The reaction mixture was held at 50−55 °C until it was at least 50% complete by HPLC analysis, and then it was heated to reflux. After quenching with water, acetonitrile and hexamethyldisiloxane were removed by azeotropic distillation, and the product was extracted into MIBK. The rich extracts were combined and washed with water to remove inorganic salts. After concentration, the product **2** was cleanly crystallized, producing **2** in good yield and excellent quality in the manufacturing start-up (Table 3). The output was cleanly converted in the next step. Subsequent campaigns demonstrated process E to be a very rugged process.

Summary and Perspective

A rugged process was developed over several iterations for the preparation of a phosphinic acid by a TMS-modified Arbuzov reaction. In the plant this process gave extremely high quality product (99.9% average purity) in good yield (82%). One key was developing an addition sequence which allowed for the safe control of exotherms, which was complicated by the fact that the reflux temperature decreased with conversion of reagents. Quantitative assessment of the reaction boiling point and exotherm led to the selection of the best addition and heating protocol. The product quality was improved by developing an organized, reproducible crystallization that led to the isolation of the product without oiling. The ruggedness of the process has been borne out with the successful production of many tons of product.

It is instructive to assess how the essential features of this process could be developed more quickly in each of the key areas, exotherm control and isolation of product. The extent of the combined exotherm of silylation and the Arbuzov reaction was not appreciated with early lab experiments, even those with process B, probably due to the relative ease with which heat is lost in uninsulated small equipment (large surface area to volume ratio). Increasing the amount of solvent used (1 L of acetonitrile/kg of **1** was chosen to increase throughput) would have provided a greater heat sink for control of the overall exotherm. With the advent of today’s sophisticated testing equipment and increased attention to safety, the exotherms associated with this reaction would be quantitated before extensive development had occurred. Recently, process B was examined using routine tests to assess the reaction hazards. The combined heats of reaction were found to be about 60 cal/g of reaction mixture, or about 240 cal/g of **1**. With quantitative data on this strong exotherm, it is possible to calculate the cooling requirements and equipment needed to contain the exotherms and vapors. Quantitative analysis is necessary to truly anticipate scale-up difficulties (See Table 5.)

Safety testing using a sealed calorimeter showed that under the conditions of process B there was a significant pressure build-up at 83 °C, indicating the formation of a volatile component which was vaporized at the reflux temperature of 74−78 °C. With that knowledge in the early stages of development, we would have examined the reaction about 20−30 °C below the reflux temperature. The extended reactions at these temperatures would have markedly increased cycle time and decreased productivity, and other conditions would have been developed with due caution.

One safe option is to conduct the silylation of **1** and chloroacetic acid separately, combine the silylated intermediates, and heat to carry out the modified Arbuzov reaction. This option was not employed due to equipment constraints, leading instead to the development of process E. In process E the exotherm was effectively controlled by extending the addition times and reaction time at temperatures below the reaction boiling point.

Boiling Point Decrease. The rapidly decreasing boiling point observed with process B was at first puzzling. Since boiling point is determined by the sum of the partial pressures of each component, the boiling point will be influenced primarily by the relative amounts of TMSCl, HMDS, silylated chloroacetic acid, CH_3CN, and the equilibrium between ammonium chloride, ammonia, and HCl. The contribution from the ammonium chloride−ammonia−HCl equilibrium is the same for processes B, D, and E. In process C, some silylation occurred before HMDS addition was completed, and thus not all HCl formed could be neutralized in situ by HMDS/NH_3. The liberated HCl would have decreased the boiling point prior to the completed addition of HMDS. As seen with process B, the boiling point fell as

***Table 5.* Thermal stability of process B**

ARC test conditns[a]	results	comments
direct heating to 78 °C followed by isothermal test at 78 °C	exotherm between 78 and 97 °C, isothermal conditions cannot be maintained	runaway due to the evaporation of solvent expected
adiabatic test, 30−300 °C	exotherm between 30 and 57 °C, slow self-heating rate, $(dT/dt)_{max} = 0.1$ °C/min	no exothermic activity above 60 °C; total heat of reaction ca. 60 cal/g of mixture
after initial exotherm, isothermal stage at 83 °C	(1) exotherm between 20 and 45 °C, slow heat rate, $(dT/dt)_{max} = 0.1$ °C/min	consistent with the heat generation data above
	(2) pressure change during isothermal stage	approximately 3.6 mL of gas per 6.4 g of reaction mixture

[a] Data generated by accelerated rate calorimeter.

the level of HMDS decreased. TMSCl was consumed by silylating both **1** and chloroacetic acid, but the regeneration of the lower-boiling TMSCl during the modified Arbuzov reaction would contribute to the depressed boiling point. The formation of trimethylsilyl chloroacetate (bp 159 °C) would contribute to raising the reaction boiling point, and as trimethylsilyl chloroacetate was consumed the boiling point should fall. These considerations are consistent with process B, in which the reflux temperature rose and fell as the reaction progressed.

Isolation/Purification. Isolation of **2** from water was initially preferred, as conscientious treatment and disposal of aqueous filtrates was easier at the time than the corresponding disposal of organic streams. Unfortunately, crystallization of **2** proceeded through an oil dispersion, and residual oil in the product crystalline suspension entrapped impurities. The oil could be displaced in routine laboratory operations, by washing the filter cake on a suction funnel. Isolation and washing using analogous conditions in the pilot plant routinely produced high-quality product in the pilot plant, and we were confident initially that suitably high quality material would be routinely provided in manufacturing batches. On manufacturing scale a polypropylene filter press was selected, as there were no centrifuges available that would hold up to the corrosive nature of these filtrates (HCl, NH_4Cl, pH <0.5). Washing on the filter press did not adequately displace the oil and residual impurities, decreasing product quality. In this case the equipment available led us to consider an alternative.

Isolating **2** from an organic solvent improved the product quality in several ways. By extracting **2** into MIBK and washing the extract with water we were able to reduce the levels of one water-soluble impurity (NH_4Cl), such that we did not need to rely upon a water wash of **2** on the filter to remove this impurity. More importantly, upon crystallization of **2** from MIBK the impurities were totally dissolved. Impurities in the mother liquor adsorbed to the wet cake were readily displaced by washing with MIBK, affording an easy purification.

In conclusion, a rugged manufacturing process was developed. Safe conditions were employed to handle the reaction exotherms and the generation of a volatile byproduct. The exotherm experienced would have been controlled more readily by diluting the reaction mixture with more solvent, or by conducting the silylations separately. Crystallization of the concentrated MIBK extract provided a final product slurry from which high-quality **2** could be readily isolated in multikilogram batches in manufacturing. Routine safety testing in place today would allow more rapid development of a safe, optimized process.

Experimental Section

General Methods. Reagent-grade solvents and reagents were used. Reaction was followed by HPLC using a 15 cm Zorbax amine column, held at 31 °C, eluted at 1.0 mL/min with 40:50:10 0.2% aqueous H_3PO_4/acetonitrile/methanol, with monitoring at 215 nm. In-process reaction aliquots were prepared by quenching 25 μL into into 10 mL of mobile phase, in order to minimize oxidation of silylated **1** to the phosphonic acid.

[Hydroxy(4-phenylbutyl)phosphinyl]acetic Acid (2). Under a nitrogen atmosphere a reactor was charged with HMDS (72.8 mL, 0.345 mol) and TMSCl (43.8 mL, 0.345 mol). In two separate vessels under nitrogen,[10] **1** (49.60 g, 0.25 mol) was dissolved in acetonitrile (25 mL), and chloroacetic acid (30.72 g, 0.325 mol) was dissolved in acetonitrile (25 mL). The chloroacetic acid solution was added to the reactor, allowing the temperature to rise to 50−55 °C, with cooling as necessary. While the reaction mixture was maintained at 50−55 °C, the solution of **1** was added over at least 3 h. When in-process HPLC analysis indicated that the amount of **2** was at least 50 area %, which usually had been reached by the end of the addition of **1**, the reaction mixture was heated to reflux (74−78 °C). When the reaction was complete, the mixture was cooled to at least 40 °C and quenched into water (100 mL) cooled to 0−5 °C. [Note: Vigorous evolution of HCl occurs with this operation.] The quenched mixture was maintained below 50 °C, and the reactor was rinsed with water (25 mL). The mixture was concentrated atmospherically until the pot temperature reached 95−97 °C. The concentrated reaction mixture was cooled to 30−35 °C and extracted with MIBK (3 × 200 mL). Any water separating from the combined organic extracts was discarded, and the rich organic phase was washed with water (3 × 75 mL). Volatile components were removed by concentrating at 50−75 °C, with appropriate adjusting of the vacuum source, until the moisture content of the concentrate was less than 0.5 vol %. Then the reactor volume was adjusted (to 320 mL) by continued concentration or addition of MIBK, and the contents were cooled to about 70 °C. The solution was seeded with **2** and held at the crystallization temperature (about 67−69 °C) for at least 30

---

[10] A nitrogen atmosphere was used to prevent absorption of atmospheric moisture during the endothermic dissolutions.

min. The suspension was cooled to 0−5 °C and held at that temperature for at least 1 h. The product was isolated by filtration, washed with MIBK (2 × 50 mL, chilled to 0−5 °C), and dried under vacuum at 40−50 °C to return **2** (53.17 g, 83%) as a white solid,[11] mp 112−113 °C (uncorrected). HPLC analysis showed 100 area % and 98.6−100% purity vs standard. ^{1}H NMR [300 MHz, DMSO-d_6] δ 1.45−1.85 (m, 6H), 2.58 (psuedo t, 2H, $J = 7.3$ Hz), 2.78 (d, 2H, $J = 17.2$ Hz), 7.14−7.30 (m, 5H), 8.53 (br s, 2H). ^{13}C NMR [75 MHz, DMSO-d_6] δ 21.1 (d, $J = 4.0$ Hz), 29.1 (d, $J = 96.2$ Hz), 32.2 (d, $J = 15.4$ Hz), 34.9, 38.1 (d, $J = 77.8$ Hz), 125.8, 128.35, 128.41, 142.1, 168.5 (d, $J = 4.3$ Hz). ^{31}P NMR [121.5 MHz, DMSO-d_6] δ 47.0. IR (KBr): 3450, 1624, 1604, 1156, 1108 cm^{-1}. Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.25; H, 6.69; P, 12.09. Found: C, 56.15; H, 6.76; P, 12.04.

Acknowledgment

We thank E. Goold, J. Byrne, and the staff at BMS, Swords, Ireland, for their tireless work on start-ups and subsequent campaigns; J. Cronin and the QC staff at BMS, Swords, for detailed analyses; C. Wei for assistance on obtaining RSST data; and M. Gardineer and M. Coradetti of New Brunswick AR&D for many replicate assays.

Received for review October 30, 1996.[⊗]

OP970202O

---

[11] Spectral and physical data were generated from a typical process E batch.

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1997.