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Development of a Scaleable Synthesis for 1,2-Bis(2-aminophenylthio)ethane (APO-Link) Used in the Production of Bismaleimide Resin

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Abstract:

The diamine reagent 1,2-bis(2-aminophenylthio)ethane is no longer commercially available but is still required for the synthesis of the bismaleimide resin, APO-BMI, used in syntactic foams. In this work, we examined the hydrolysis of benzothiazole followed by reaction with dichloroethane or dibromoethane. The deprotonation of 2-aminothiophenol followed by reaction with dibromoethane was also investigated and later optimized for scale-up by scrutinizing all aspects of the reaction conditions, work-up, and recrystallization. On bench-scale, the optimized procedure consistently produced a 75–80% overall yield of finely divided, high purity product (>95%). The material was also produced on both a 100 lb scale and a 200 lb scale using the optimized process, giving high quality material in excellent yield.

Introduction

Aromatic diamine reagents have been used for decades in weapon systems as starting materials for urethane elastomers and bismaleimide resins. In the 1970s, two commonly used aromatic diamines, methylenedianiline (MDA; Figure 1) and 4,4′-methylenebis(2-chloroaniline) (MOCA or MBOCA; Figure 2) were ruled to be possible carcinogens.[1] At the time, a three-phase syntactic foam called Kerimid 601 was used and consisted of a mixture of MDA, 4,4′-bismaleimidodiphenylmethane (BMI; Figure 1) bismaleimide resin and glass microballons (GMB).[2–5] Uncured Kerimid 601 consisted of a weight ratio of approximately 6.7 parts BMI to 1 part MDA.[2] In addition, an important urethane elastomer system based on MOCA and Adiprene L-100 prepolymer (Figure 2) was widely used. The carcinogen rulings led to extensive replacement programs for both materials.

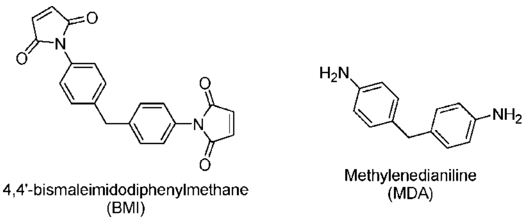

Figure 1. **Structures of 4,4′-bismaleimidodiphenylmethane (BMI) bismaleimide resin and methylenedianiline (MDA).**

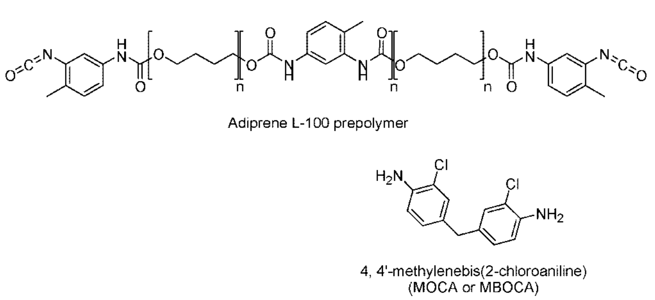

Figure 2. **Structures of Adiprene L-100 prepolymer and 4,4′-methylenebis(2-chloroaniline) (MOCA or MBOCA).**

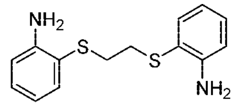

Figure 3. **Structure of 1,2-bis(2-aminophenylthio)ethane.**

During the late 1970s, research indicated that 1,2-bis(2-aminophenylthio)ethane, known commercially as APOCure-601 (Figure 3), was a promising replacement for MOCA in some urethane systems.[6] In the early 1980s, 1,2-bis(2-aminophenylthio)ethane, then known as Cyanacure, was used as a diamine curing agent for urethane adhesives containing Adiprene L-100.[7] During this same period, 1,2-bis(2-aminophenylthio)ethane was also used as the diamine reagent for the

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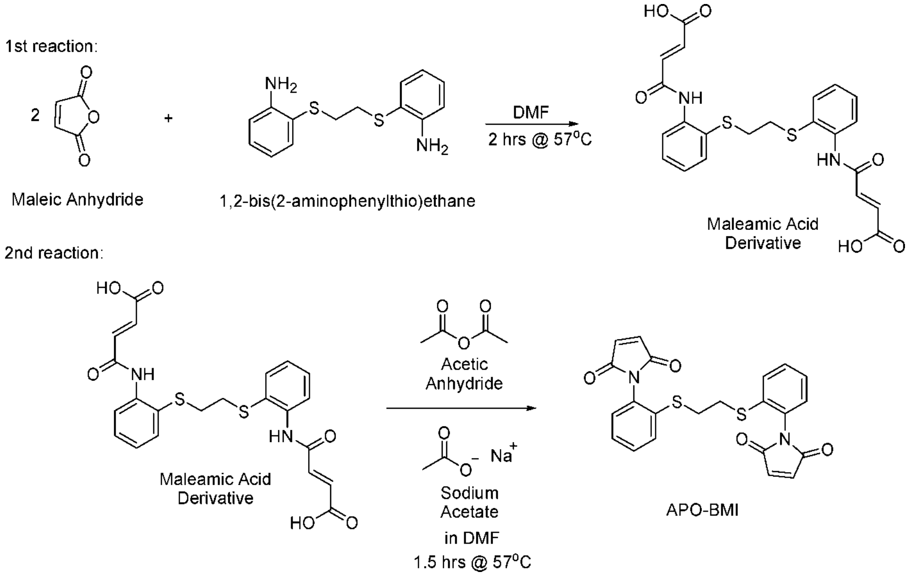
Scheme 1. **Synthesis of APO-BMI resin from 1,2-bis(2-aminophenylthio)ethane (APO-Link) and maleic anhydride**



formation of the new bismaleimide resin, APO-BMI, the replacement for Kerimid 601 (Scheme 1).[8] American Cyanamid sold 1,2-bis(2-aminophenylthio)ethane under the trade name Cyanacure until 1989 when it was discontinued.[9] In the 1990s, 1,2-bis(2-aminophenylthio)ethane reappeared on the market under the name Versalink C138 from Air Products, but was once again discontinued. Currently, 1,2-bis(2-aminophenylthio)-ethane is not commercially available in any significant quantity.

Because the material is no longer commercially available, it will be manufactured in-house at Honeywell's Kansas City Plant (KCP). In this work, we have focused on the bench-scale optimization of 1,2-bis(2-aminophenylthio)ethane in preparation for scale-up in the Polymer Production Facility at KCP. The diamine reagent has been granted yet another name, APO-Link, and will be used in the production of the bismaleimide resin, APO-BMI.

The goal of the synthetic development of APO-Link was to optimize a procedure that was suitable to a 100 gallon or larger scale. Important factors for scale-up included utilizing practical methods, reducing processing time, reducing reaction volumes, increasing yields, minimizing equipment requirements, and taking ES&H concerns into account.

There are two basic approaches to the synthesis of 1,2-bis(2-aminophenylthio)ethane (APO-Link). The first approach is documented in a U.S. Patent from 1975 and involves the hydrolysis of benzothiazole with sodium hydroxide followed by reaction with dichloroethane.[10] Although the crude yield is reported to be 98%, the purified yield and crystallization solvent were not reported. An alternate approach is reported in the literature and involves deprotonation of 2-aminothiophenol (ATP) with sodium ethoxide.[11–13] A typical procedure involves adding dibromoethane dropwise to a refluxing solution of 2-aminothiophenol and sodium in anhydrous ethanol. The mixture is then allowed to cool to room temperature and added to ice–water to precipitate the crude material. Following crystallization in ethanol, the purified yield is typically 70–80%. For scale-up, there are obvious concerns with using sodium in ethanol followed by precipitation in water. An important note is that the pK_a of 2-aminothiophenol is 6.6–6.8,[14,15] which means that it is possible to replace sodium ethoxide with other bases in this approach.

By altering the starting materials and reaction conditions, we pursued five basic reaction paths (Scheme 2) toward the synthetic optimization of APO-Link. Synthesis work was completed in laboratory glassware at Los Alamos National Laboratory (LANL) as well as a fully instrumented 1 L reaction calorimeter at KCP.

Results and Discussion

Prior to our synthetic work, we conducted a detailed characterization of 1,2-bis(2-aminophenylthio)ethane samples previously available from American Cyanamid as "Cyanacure" and later from Air Products as "Versalink C138" to provide baseline data (Figure 6). A detailed discussion of our results can be found in the Supporting Information.

Because the synthesis of APO-Link will be scaled to a 100 gallon or larger reactor, every aspect of the bench-scale synthesis was scrutinized and optimized if possible. The goal was to maximize the yield using an efficient process where reagents, solvents, waste, and corrosion were minimized. Table 1 summarizes the results of bench-scale APO-Link reactions performed at LANL and KCP.

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Scheme 2. **Synthesis of APO-Link from the hydrolysis of benzothiazole or deprotonation of 2-aminothiophenol (ATP) followed by reaction with dichloroethane (DCE) or dibromoethane (DBE)**

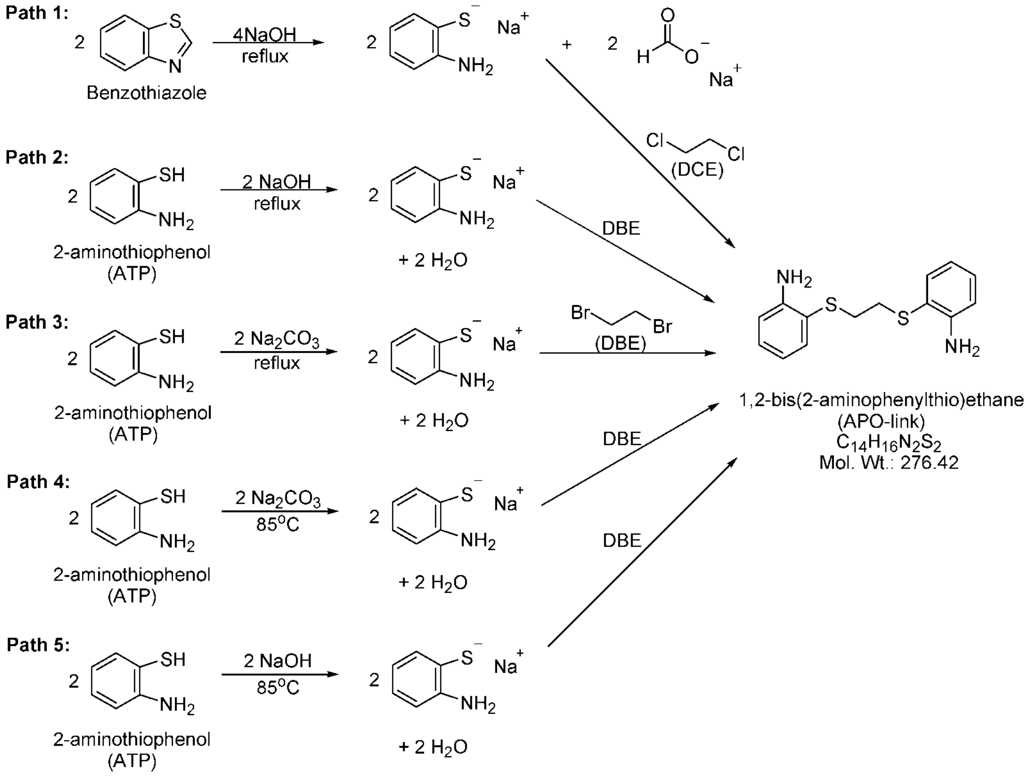

Table 1. **Purity values of bench-scale APO-Link reactions**[a]

reaction	condition	work-up method	crude yield (%)	rextal method	GC/MS %APO-Link	GPC %APO-Link
A	Path 1	1	56	1	96.23	
B	Path 1	2	80	1	94.57	
C	Path 1	2	80	3	98.44	
D	Path 1	3	60	2	87.40	
E	Path 1	2	79	2	90.57	
F	Path 1 (w/DBE)	4	90	4	87.56	
G (2.0 mol benzothiazole)	Path 1	5	*b*	5		96.00
H (2.0 mol benzothiazole)	Path 1	5	70	5		93.90
I	Path 2	4	89	4	85.82	
J	Path 2	4	89	4	89.12	
K	Path 2	4	89	5	93.70	
L (2.0 mol ATP)	Path 2	5	93	6		92.30
M (6.0 mol ATP)	Path 2	5	90	6		93.82
N	Path 3	4	92	5	98.38	
O	Path 3	4	93	5	97.21	
P	Path 4	4	93	5[c]	71.62	
Q	Path 4 (w/DCE)	4	83	5	96.56	
R (1.0 mol ATP)	Path 4	4	92	5	97.25	94.6
S (2.0 mol ATP)	Path 5 (DBE addn. 45 min)	5	88	5[c]	98.07	97.22
T (2.0 mol ATP)	Path 5 (DBE addn. 45 min)	5	88	6	97.77	97.95
U (2.0 mol ATP)	Path 5	5	*b*	6	99.3	97.80
V (2.0 mol ATP)	Path 5 (DBE addn. 60 min)	5	*b*	6	98.04	97.42
W (2.0 mol ATP)	Path 5 (DBE addn.180 min)	5	*b*	6	96.76	95.43
X (2.0 mol ATP)	Path 5 (DBE addn. 60 min; rextal after 2nd rinse)	5	*b*	6	98.04	95.79

[a] Reaction scales are based on 0.10 moles benzothiazole or ATP unless otherwise noted. Crude yield percentage is based on calculated theoretical yield. [b] Total crude product was not isolated and dried. [c] After dropwise addition of water, the recrystallization solution was stirred during cooling.

Synthesis Process. The initial work focused on the hydrolysis of benzothiazole using sodium hydroxide followed by the reaction with dichloroethane (Path 1). The reaction was conducted at reflux and is described in U.S. Patent 3,920,617 from 1975. We used dichloroethane but also studied this reaction using a more reactive reagent, dibromoethane. Replacing dichloroethane with dibromoethane increased the yield and purity of the crude product. Other synthetic options were considered due to the corrosive nature of Path 1. An alternate approach reported in the literature, involves deprotonation of

2-aminothiophenol (ATP) with sodium ethoxide.[11–13] For scale-up, the use of elemental sodium in ethanol is not practical. The pK_a of 2-aminothiophenol is 6.6–6.8,[14,15] allowing for the replacement of sodium ethoxide with more mild bases using this approach. Example 1 of U.S. Patent 3,920,617 describes the deprotonation of ATP with sodium hydroxide followed by reaction with dichloroethane.[10] We successfully used both sodium hydroxide and sodium carbonate to deprotonate ATP. In comparison to Path 1, this approach is more attractive, requiring less base and completely consuming all starting materials. Using sodium carbonate (Na_2CO_3) is appealing because it is less corrosive than sodium hydroxide. However, from a scale-up standpoint, the overall volume of the reaction can be reduced by using NaOH because it has a higher solubility in water. At 20 °C the solubility of NaOH is 111 g/100 mL, whereas the solubility of Na_2CO_3 in water is 30 g/100 mL. Thus, corrosion issues were outweighed by production scale limits. We further reduced the corrosive nature of the reaction by lowering the reaction temperature to 80–85 °C from reflux.

Work-Up/Extraction. One processing hurdle involved the work-up or extraction of the crude product. The crude material quickly solidified into a hard, yellow wax (mp 50–65 °C), thus presenting major complications when conventional bench-scale work-up methods (such as a separatory funnel extraction) were employed. A considerable amount of time was devoted to devising a work-up method that would minimize solvent amounts and the loss of the crude material while effectively removing salts from the thick, molten wax. Five methods for work-up/extraction were studied during bench-scale work. Details of each method can be found in the Supporting Information. The five methods were the following: (1) boiling water extraction in separatory funnel; (2) organic/aqueous extraction with methyl ethyl ketone (MEK) and water; (3) water extraction at room temperature; (4) repeat extraction and cooling; (5) hot water extraction in reactor with drain.

Method 5 was the most practical for scale-up. For reactions performed in the 1 L reaction calorimeter or jacketed cylindrical reactor, work-up was completed in the reactor because a bottom outlet drain was available. When the second reaction was completed, the layers were allowed to separate, while the reactor temperature set point was maintained at approximately 85 °C. Due to the high salt content, the aqueous layer was on the bottom and was drained from the reactor. Hot water was added to the reactor for the rinsing step. Following phase separation, the organic crude material (now bottom layer) was quickly drained from the reactor and then returned after the aqueous portion was removed. This process was repeated to give a total of three rinses. Although this method of extraction is fairly common in plant facilities, the hard, waxy nature of the crude material provided the potential for significant complications during large-scale extraction and transfer. An understanding of the material's behavior during bench-scale optimization proved extremely valuable when preparing for large-scale optimization. Equipment modifications accounted for the need to keep the dense waxy material molten and piping was designed to prevent solidification during transfer. Our method provides an optimized extraction of salts from the molten wax with minimal hot water and no organic solvents.

Recrystallization/Purification. Another processing hurdle involved purification of the crude product via recrystallization. In U.S. Patent 3,920,617, example 2 (using Path 1 chemistry) does not report the recrystallization solvent or yield. In early Path 1 reactions, the crude product was recrystallized from ethanol based on additional literature references.[11–13] However, ethanol was not a very efficient solvent for recrystallization because the crude product was fairly soluble at room temperature. Additional solubility and recrystallization information can be found in the Supporting Information. Using typical bench-scale recrystallization techniques, the purified APO-Link crystallized in a dense, crystalline cake. In this form, the material would have been impossible to remove from a large-scale reactor, costing both time and yield. Solvent combinations and techniques were used to yield a slurry of recrystallized product that could be transferred for filtration and drying, thus avoiding "caking" of the purified product. A considerable amount of time was devoted to devising a recrystallization method that would minimize solvent, give high purity, and yield a material consistency conducive for transfer, processing, and drying. We also wanted to purify the material in the same reactor used for synthesis and extraction, thus reducing the need for material transfer. Both denatured and nondenatured ethanol resulted in successful recrystallizations. Recrystallization of the crude material was investigated using six different solvent conditions:

1. 100% Ethanol. Although used in the literature, ethanol is not a very efficient solvent for large-scale recrystallization because the crude product is fairly soluble at room temperature. Although the purity levels were good, the yield of the first crop of material was only about 25–35% based on the amount of crude used. Several crops of material must be isolated from the solution to maximize the overall yield, making the recrystallization very time intensive.

2. Ethanol/Water 95/5 (v/v). The crude product is still considerably soluble in this solvent combination at room temperature.

3. Ethanol/Water 50/50 (v/v). Approximately 900 mL of hot 50/50 (v/v) ethanol/water was required for the recrystallization of about 11 g of crude product. Although the purity levels were quite good, the ratio of solvent to crude product is too large to be practical for scale-up.

4. Ethanol/Water 80/20 (v/v). The crude product is largely insoluble at room temperature but dissolves in a reasonable amount of hot solvent. When 80/20 (v/v) ethanol/water was used, the yield of the first recrystallized crop from the crude material was improved to approximately 70% compared to only 25–35% yield for the first recrystallized crop from 100% ethanol or 95/5 (v/v) ethanol/water.

5. Ethanol Followed by Dropwise Addition of Water. Attempts to further reduce the total solvent volume were made by dissolving the crude material in a minimal amount of hot ethanol and seeding the crystallization by adding water dropwise. This method worked quite well, however, the problem of "caking" was still observed.

6. Constant Agitation Method. Although good recrystallized recovery and purities were achieved with the previous two methods, it was still imperative to obtain the purified material in a form that could be easily transferred and dried on large

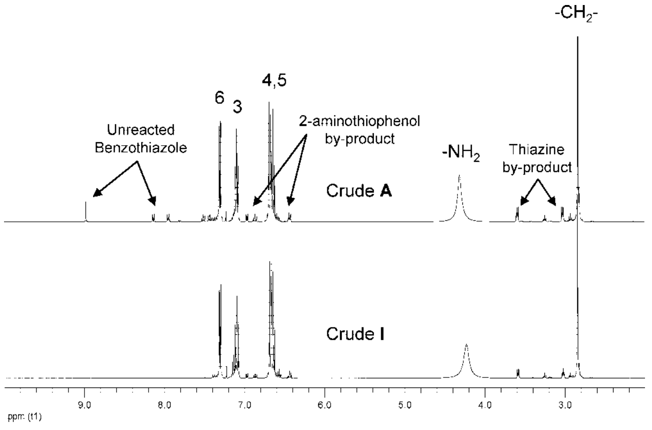

Figure 4. **^{1}H NMR of crude APO-Link product A (Path 1) and product I (Path 2) and identification of impurities.**

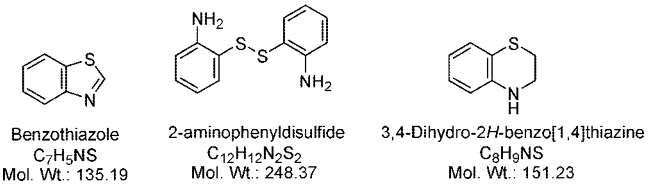

Figure 5. **Major impurities in crude APO-Link products from path 1.**

Table 2. **Metal content of APO-Link samples prepared in Hastelloy vessel**[a]

Sample	Ni (mg/kg)	Mo (mg/kg)	Cr (mg/kg)
KCP - 04062005	86.0	37.4	nd[b]
KCP - 05182005	136.8	8.8	nd[b]

[a] Concentration is average of triplicate analyses. [b] nd = not detected.

scale. Stirring during recrystallization is contrary to conventional bench-scale chemistry techniques but is a normal method for large-scale crystallizations. Using the optimized solvent combination, rapid stirring of the solution during cooling allowed for uniform temperature distribution and yielded a slurry of recrystallized APO-Link. The slurry could be efficiently transferred, filtered, and dried. Both 80/20 ethanol/water by weight (w/w) and by volume (v/v) were used in the bench-scale development, with no observable differences in the final product. Because it is more practical to weigh large amounts of solvents, the weight percent method for preparation of 80/20 ethanol/water solution was chosen for synthesis scale-up. In terms of feasibility for scale-up, the constant agitation method was a considerable improvement over more conventional bench-scale methods examined and consistently yielded high purity material in 75–80% overall yield. On bench-scale, the recrystallization slurry was cooled to 0 °C in order to maximize product recovery. Existing equipment in the Polymer Production Facility does not have the capability to conveniently cool to this temperature; therefore, the temperature dependence of the product recovery was studied. It was found that the majority of the purified APO-Link crystallized at 40 °C (see Supporting Information). Therefore, for the full-scale production, existing equipment was used to cool the recrystallization slurry to 25 °C with constant agitation and resulted in 75% overall reaction yield on both the 100-lb and the 200-lb scale. The effect of cooling rate on the APO-Link material was also examined. There was not a considerable difference in the particle size of the material when cooled at a very fast rate (50°/h) versus a very slow rate (3°/h) with similar agitation conditions.

APO-Link Impurities. Both GC/MS and NMR spectroscopy (Figure 4) were used to characterize the starting materials, crude products, recrystallized products, and organic material remaining in aqueous extracts. The major impurities arising from the hydrolysis of benzothiazole followed by reaction with dichloroethane (Path 1) appear to be unreacted benzothiazole, 2-aminophenyldisulfide and 3,4-dihydro-2*H*-benzo[1,4]thiazine (Figure 5). The crude materials from reactions with 2-aminothiophenol (Paths 2–5) were also examined. Using ^{1}H NMR, there was no evidence of the starting material, 2-aminothiophenol. The major impurities arising from the deprotonation of 2-aminothiophenol followed by reaction with dibromoethane (Paths 2–5) appear to be 2-aminophenyldisulfide and 3,4-dihydro-2*H*-benzo[1,4]thiazine.

Corrosion Study of APO-Link Synthesis. A major concern of this synthetic process was the corrosive nature of the APO-Link reactions, especially Paths 1 and 2, where concentrated aqueous sodium hydroxide solutions at reflux are used. During early bench-scale development at KCP, equipment constructed of glass was damaged due to base corrosion. In addition, crude APO-Link samples synthesized in a nickel alloy reactor clearly showed evidence of nickel and molybdenum (Table 2).

The existing 100 gallon reactors at KCP's Polymer Production Facility are lined with glass. Reactor A is lined with Pfaudler 3115 multipurpose glass, and reactor D is lined with DeDietrich 3009 multipurpose glass. Glass coupons of each type were acquired from the manufacturer and exposed to the bench-scale reaction conditions. Worst-case scenario glass lifetime estimates were calculated based on thickness measurements. Under Path 1 conditions, the effects of corrosion were substantial, and the worst-case lifetime of the Pfaudler 3115 glass was determined to be approximately 8 years. Under Path 2 conditions, the effects of corrosion were less pronounced. The worst-case lifetime of the Pfaudler 3115 glass was roughly 35–40 years. The DeDietrich 3009 glass did not show any discernible thinning under Path 2 conditions; thus, the lifetime was unlimited. Because our final optimization uses sodium hydroxide at 85 °C (Path 5), there are even fewer concerns over reactor corrosion and damage. Reactor D lined with DeDietrich 3009 multipurpose glass was chosen for APO-Link production.

Reaction Calorimetry Data for Scale-Up. Power compensation calorimetry was also used to study the optimized bench-scale procedure to provide additional data for scale-up. Prior to scale-up of Path 5 chemistry, power compensation calorimetry was used to accurately measure the molar heat of reaction during the addition of ATP (1st reaction) and the addition of 1,2-dibromoethane (2nd reaction). During the addition of ATP in the first reaction, the molar heat of reaction was 43.23 kJ/mol. During the addition of dibromoethane in the second phase of the reaction, the molar heat of reaction was 214.79 kJ/mol. This information was needed prior to full-scale production in order to assess heat removal requirements.

Addition Rate and Rinsing. The addition rate of DBE was investigated prior to scale-up (Table 1) because the addition of

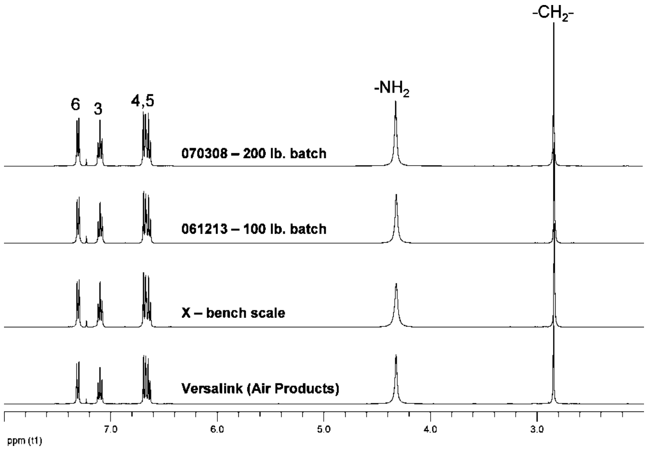

Figure 6. **^{1}H NMR spectra of Versalink (formerly available from Air Products), recrystallized product X from optimized bench-scale procedure, and recrystallized product from 100 lb and 200 lb production scale.**

DBE is the most exothermic portion of the synthetic process. In **V**, DBE was added over 60 min, and in **W**, DBE was added over 180 min. There was no significant difference in the overall yield and purity between the two reactions. Thus, a 60 min addition time of DBE was recommended to reduce overall processing time. In **X**, the third water rinse was eliminated to determine if the overall cycle time could be reduced. Because the yield and purity of the recrystallized product following the second rinse were quite good, it may be possible to eliminate the third hot water rinse during large-scale production. Although not surprising, we also found that the purity of the recrystallized product could be increased slightly simply by carrying out an additional rinse of the recrystallized product with chilled 80/20 (w/w) ethanol/water. This option may be useful if the material requires large-scale rework to meet material specifications.

Scale-Up. The synthesis of APO-Link was scaled up using Path 5 conditions in a 100 gallon reactor lined with DeDietrick 3009 multipurpose glass. The material was produced on approximately 100 lb (batches **061115** and **061213**) and 200 lb (batch **070308**) scales. The material was recrystallized with agitation within the same 100 gallon glass-lined reactor. The slurry was transferred to a 50 gallon Pfaudler Nutsche filter dryer for filtration and final drying. The thick product slurry was transferred using a streamlined transfer design with 2-in diameter piping. The overall yields of the large-scale production batches were approximately 75% of free-flowing, finely divided material, with a purity of 96–99%, using both GPC and GC/MS. We also used NMR spectroscopy to verify the high quality of APO-Link material produced on both bench scale and production scale (Figure 6). The ^{1}H NMR spectra are identical for the optimized bench-scale sample **X**, the 100 lb scale production batch **061213**, and the 200 lb production scale batch **070308**. Furthermore, the spectra match ^{1}H NMR of Cyanacure and Versalink samples that were previously commercially available.

Conclusion

The recommended procedure for the scaled-up synthesis of APO-Link is based on the deprotonation of 2-aminothiophenol, with sodium hydroxide at 80–85 °C, followed by addition of dibromoethane. The molten crude product is rinsed multiple times with hot water and then recrystallized with 80/20 (w/w) ethanol/water solution. Our optimized procedure consistently gives 75–80% overall yield of product, with a purity greater than 95% purity by GC/MS. Our work has provided valuable characterization information for the material specification along with a scalable procedure for APO-Link production. APO-Link has been produced on both 100 lb and 200 lb scales, using the optimized process, giving high quality material in excellent yield. The synthetic optimization of APO-Link involved collaboration between chemistry and engineering from the initial development. Our work clearly illustrates the importance of constant collaboration between laboratory and pilot-plant to develop a practical synthetic process for scale-up.

Experimental Section

General. Benzothiazole (Aldrich, 96%), 2-aminothiophenol (Aldrich 99% or Alfa Aesar 98%), 1,2-dichloroethane (Aldrich 99%), 1,2-dibromoethane (Aldrich 99+%), sodium hydroxide (Fisher 99% or Acros 98%), sodium carbonate (Fisher 99%), methyl ethyl ketone (Acros 99+%), and ethanol (AAPER, nondenatured, Absolute 200 proof or 190 proof). All reagents were used as received without additional purification.

For nuclear magnetic resonance spectroscopy (NMR), samples were prepared by dissolving approximately 30 mg of APO-Link sample in 0.8 mL of deuterated chloroform ($CDCl_3$ 99.8 atom % D with 1% v/v TMS). A Bruker Avance 400 spectrometer was used for proton and carbon NMR analysis (operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C). For ^{1}H, 16 scans were collected and for ^{13}C, at least 176 scans were collected. All spectra were referenced against TMS at 0 ppm. For Fourier transform infrared spectroscopy (FT-IR), samples for solution FT-IR were prepared by dissolving approximately 50 mg of sample in 3.0 mL of carbon tetrachloride (CCl_4, 99.9% ACS reagent). The solution was then injected into a SL-3 KBr solution cell with a 0.1023 mm pathlength (International Crystal Laboratories). A Mattson 5000 Series FT-IR spectrometer was used for the analysis. Before spectra were collected, a background spectrum of carbon tetrachloride was collected and stored. All spectra were collected with 16 scans from 4000 cm^{-1} to 850 cm^{-1}, with a resolution of 2 cm^{-1}. After analysis of each sample, the solution cell was thoroughly rinsed with carbon tetrachloride and evacuated to prevent cross-contamination of samples. Samples for solid FT-IR analysis were prepared by fabricating a solid potassium bromide pellet using approximately 7 mg of sample and 350 mg of KBr. A Mattson 5000 FT-IR spectrometer was used for the analysis. Before spectra were collected, a background spectrum was collected and stored. All spectra were collected from 4000 cm^{-1} to 400 cm^{-1}, with a resolution of 2 cm^{-1} and 16 scans. For gas chromatography coupled with mass spectrometry (GC/MS), samples were prepared by dissolving 0.20 g of sample in 9.7 g of acetonitrile with 0.1 g of a 1% diglyme internal standard solution in acetonitrile. An Agilent 5890 gas chromatograph with a 5971 mass spectrometer was used. The separation of APO-Link components resulted in a total ion chromatograph (TIC). The peaks were identified through retention time matching and comparison to mass spectra. The GC/MS column was a Restek Rtx-5 30 m × 0.25 mm i.d. × 0.25 μm film. The injection port temperature was 250 °C. The sample was injected with split injection mode, consisting of a 1 μL injection with an 8:1 split flow ratio. The oven temperature was 50 °C, with a ramp of 10 °C/min to 280 °C followed by an isotherm at 280 °C for 20 min. The MS transfer temperature was 280 °C. The relative area % quantitation was performed by summing all the peak areas and then dividing the area of each peak by the total peak area. This gives a relative concentration and requires no standards. Using these conditions, the retention time of APO-Link was approximately 26.8 min. For gel permeation chromatography (GPC), samples were prepared by dissolving approximately 20 mg of sample in 10 mL of tetrahydrofuran (THF stabilized with BHT). Stabilized THF was used as the mobile phase with three Waters high-resolution HR0.5 columns arranged in series. The molecular weight range for this type of high-resolution column is 0–1000 g/mol. The high-resolution columns are cross-linked styrene/divinyl benzene with ~60 Å pore size. As with GC/MS, the GPC quantitation was performed using a relative area % method. For inductively coupled plasma spectroscopy (ICP), approximately 250 mg of sample was digested under agitation at ambient temperature in 10 mL of 50% (v/v) concentrated HNO_3 for approximately 24 h. The sample was filtered first through a 5 μm syringe filter and then filtered a second time through a 0.45 μm syringe filter. The sample was diluted with deionized water to give a final sample concentration of either 0.25 mg/mL or 10 mg/mL (1% sample). The sample was analyzed for Cr, Fe, Mo, and Ni content against a certified multi-element reference standard. A nonquantitative survey scan for 66 other metals was also performed. A Thermo Jarrell Ash Corporation IRIS Inductively Coupled Argon Plasma Emission Spectroscopy system was used for the analysis. The argon plasma was operated at 1.0 kW power, with a plasma flow rate of 15.0 L/min and a nebulizer flow rate of 1.5 L/min. The vertical and horizontal slits were set at 300 and 50 mm. The viewing height above the load coil was set at 15 mm for all species. Data from the spectrometer was collected by TJA ThermoSpec-CID software. Three replicate analyses were performed for each sample, with the mean concentration reported.

General Reaction Conditions with Benzothiazole (Path 1). For experiments conducted at LANL in laboratory glassware, a mixture of benzothiazole (0.100 mol), sodium hydroxide (NaOH, 0.205 mol), and 23 mL of deionized water was heated to reflux for 4–4.5 h. The mixture was allowed to cool to 60–65 °C, and dichloroethane (DCE, 0.050 mol) was added dropwise over 20–30 min. The mixture was then heated to reflux for 2 h. Following work-up, the crude product was recrystallized and characterized.

For experiments conducted at KCP in the reaction calorimeter, 250 mL of demineralized water and sodium hydroxide (NaOH, 2.27 mol) were charged to the 1 L reactor vessel. Benzothiazole (1.13 mol) was fed to the reactor over a period of 15 min. The reaction progressed for 4 h at 116 °C. Dichloroethane or dibromoethane (DCE/DBE, 0.57 mol) was then added to the reactor over a period of 20 min. The reaction progressed for 2 h at 105 °C. Following work-up, the crude product was recrystallized and characterized.

General Reaction Conditions with 2-Aminothiophenol (Paths 2 and 3). A mixture of 2-aminothiophenol (ATP, 0.100 mol), sodium hydroxide or sodium carbonate ($NaOH/Na_2CO_3$, 0.103 mol), and 60 mL of deionized water was heated to reflux for 30 min. The mixture was allowed to cool to 60–65 °C, and dibromoethane (DBE, 0.050 mol) was added dropwise over 20–30 min. The mixture was then heated to reflux for 1.5–2 h. Following work-up, the crude product was recrystallized and characterized.

For experiments conducted at KCP in the reaction calorimeter, 215 mL of demineralized water and sodium hydroxide (NaOH, 2 mol) were charged to the 1 L reactor vessel. 2-Aminothiophenol (ATP, 2 mol) was added to the reactor over a period of 30 min. The reaction progressed for 30 min at 116 °C. Dichloroethane or dibromoethane (DCE/DBE, 1 mol) was then fed to the reactor vessel over a period of 60 min. The reaction progressed for 1.5 h at 105 °C. Following work-up, the crude product was recrystallized and characterized.

General Reaction Conditions with 2-Aminothiophenol (Paths 4 and 5). A mixture of 2-aminothiophenol (ATP, 0.100 mol), sodium hydroxide or sodium carbonate ($NaOH/Na_2CO_3$, 0.103 mol), and 60 mL of deionized water was heated at 80–85 °C for 30 min. Without additional cooling, dibromoethane (DBE, 0.050 mol) was added dropwise over 20–30 min. The mixture was then heated at 80–85 °C for 1.5–2 h. Following work-up, the crude product was recrystallized and characterized.

For experiments conducted at KCP in the reaction calorimeter, 215 mL of demineralized water and sodium hydroxide (NaOH, 2 mol) were charged to the 1 L reactor vessel. 2-Aminothiophenol (ATP, 2 mol) was added to the reactor over a period of 30 min. The reaction progressed for 30 min at 85 °C. Dichloroethane or dibromoethane (DCE/DBE, 1 mol) was then fed to the reactor vessel over a period of 60 min. The reaction progressed for 1.5 h at 85 °C. Following work-up, the crude product was recrystallized and characterized.

Detailed Optimized Procedure Based on Path 5. The optimized procedure intended for scale-up was carried out on the bench scale to verify the full-scale formulation and procedure. Deionized water (225 mL) was added to a 1 L, four-neck, cylindrical, jacketed reactor with bottom outlet. Sodium hydroxide (2.02 mol, Acros Organics 98%, 82.42 g) was transferred slowly with stirring to dissolve. The reactor jacket temperature was adjusted to maintain a solution temperature of 85 ± 5 °C. 2-aminothiophenol (2.0 mol, Aldrich 99%, 252.88 g) was transferred to a pressure-equalizing funnel for addition. The ATP was added to the sodium hydroxide solution over 30 min while maintaining the temperature at 85 ± 5 °C. Following the addition of ATP, the mixture was allowed to stir at 85 ± 5 °C for 30 min. 1,2-Dibromoethane (1.0 mol, Aldrich 99%, 187.74 g, 87.04 mL) was transferred into a graduated pressure-equalizing addition funnel. 1,2-Dibromoethane (DBE) was added to the reaction mixture over 60 min while maintaining the temperature at 85 ± 5 °C. This step was noticeably more exothermic; therefore, the temperature and addition rate were closely monitored. Following the addition of DBE, the mixture reacted with agitation at 85 ± 5 °C for 90 min. Agitation was stopped, and the phases were allowed to separate. During phase separation and work-up, the temperature was maintained at 85

± 5 °C to keep the crude product molten. Due to the high salt content of the aqueous phase, the organic fraction is the top layer in the initial phase separation. The aqueous layer was drained from the reactor and discarded. Approximately 260 mL of hot deionized water was added to the reactor, and the mixture was agitated for approximately 15 min (first rinse). Agitation was stopped, and the phases were allowed to separate for 5–10 min. The organic crude material (now bottom layer) was quickly drained and then returned to the reactor after the aqueous portion was removed. This process was repeated two more times to give a total of three rinses. The organic crude product was stirred in the reactor at a temperature of approximately 75 °C to keep the crude molten. For recrystallization, approximately 500 mL of 80/20 (w/w) ethanol/water was heated near boiling. The hot solvent was carefully poured into the reactor to dissolve the crude material. The solution was stirred for approximately 45 min to ensure complete dissolution. The temperature of the recirculating water in the reactor jacket was adjusted to 20.0 °C so the reactor would begin to cool. The temperature of the recrystallization solution and recirculating water were monitored as the solution cooled and crystallization began. Rapid stirring was maintained throughout the cooling and crystallization so that the purified product would not "cake out" within the reactor. When the recrystallization solution reached approximately 60 °C, finely dispersed solid began to come out of solution. At approximately 40 °C, the mixture was a relatively thick slurry of fine, light-yellow solid. The slurry was cooled to approximately 20–25° while stirring. Upon reaching room temperature, the mixture was poured into a Buchner funnel and vacuum filtered. During filtration, the solid was rinsed with approximately 500 mL of chilled (approximately 5 °C) 80/20 (w/w) ethanol/water. The material was transferred to a large dish and dried under reduced pressure at 45 °C for 48 h. The final dried material was a powdery, light-yellow solid (approximately 80% overall yield).

APO-Link characterization: FW (calcd) 276.42 g/mol, generally light-yellow granular powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.85 (s, 2H, CH_2), 4.33, (s, 2H, NH_2), 6.63, 6.64, 6.66, 6.67, 6.68, 6.70 (mult, 2H, aromatic H at positions 4 and 5), 7.09, 7.11, 7.13 (t, 1H, aromatic H at position 3), 7.30, 7.31, 7.32, 7.33 (dd, 1H, aromatic H at position 6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 34.4 (CH_2), 114.9 (aromatic C at position 3), 116.6 (aromatic C at position 6), 118.5 (aromatic C at position 4), 129.9 (aromatic C at position 5), 136.1 (aromatic C at position 1), 148.5 (aromatic C at position 2); IR (KBr pellet, cm^{-1}) 3366, 3358, 3290, 3182, 2062, 2931, 1617, 1583, 1479, 1446, 1423, 1316, 1304, 1288, 1249, 1206, 1164, 1096, 1058, 962, 938, 858, 837, 749, 700.

Supporting Information Available

Additional information and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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