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Bench-Scale Synthetic Optimization of 1,2-bis(2-aminophenylthio)ethane (APO-Link) Used in the Production of APO-BMI Resin

Federal Manufacturing & Technologies

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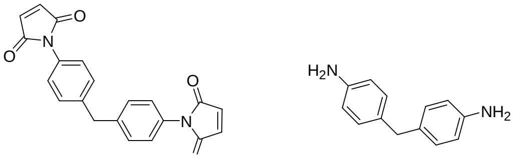
Abstract

The diamine reagent 1,2-bis(2-aminophenylthio)ethane is no longer commercially available but 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 the by reaction with dichloroethane or dibromoethane. We also studied the deprotonation of 2-aminothiophenol followed by the reaction with dibromoethane. We optimized the latter for scale-up by scrutinizing all aspects of the reaction conditions, work-up and recrystallization. On bench-scale, our optimized procedure consistently produced a 75-80% overall yield of finely divided, high purity product (>95%).

Discussion

Background

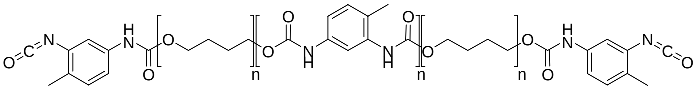
Aromatic diamine reagents have been used for decades in weapon systems as starting materials for urethane elastomers and bismaleimide resins. In the 1970s, two commonly used aromatic diamines, methylenedianiline (MDA) and 4,4'-methylenebis(2-chloroaniline) (MOCA or MBOCA) were ruled to be possible carcinogens.[1] At the time, a three-phase syntactic foam called Kerimid 601 was used and consisted of a mixture of MDA, 4,4'-bismaleimidodiphenyl-methane (BMI) 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 was widely used. The carcinogen rulings led to extensive replacement programs for both materials.



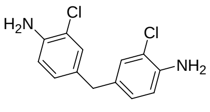
4,4'-bismaleimidodiphenylmethane (BMI)

Methylenedianiline (MDA)

Figure 1. Structures of 4,4'-bismaleimidodiphenyl-methane (BMI) bismaleimide resin and methylenedianiline (MDA).



Adiprene L-100 prepolymer

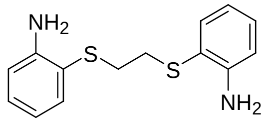


4, 4'-methylenebis(2-chloroaniline) (MOCA or MBOCA)

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

During the late 1970s, research indicated that 1,2-bis(2-aminophenylthio)ethane, known commercially as APOCure-601, 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 formation of the new bismaleimide resin, APO-BMI, the replacement for Kerimid 601.[8] American Cyanamid sold 1,2-bis(2-aminophenyl-thio)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.

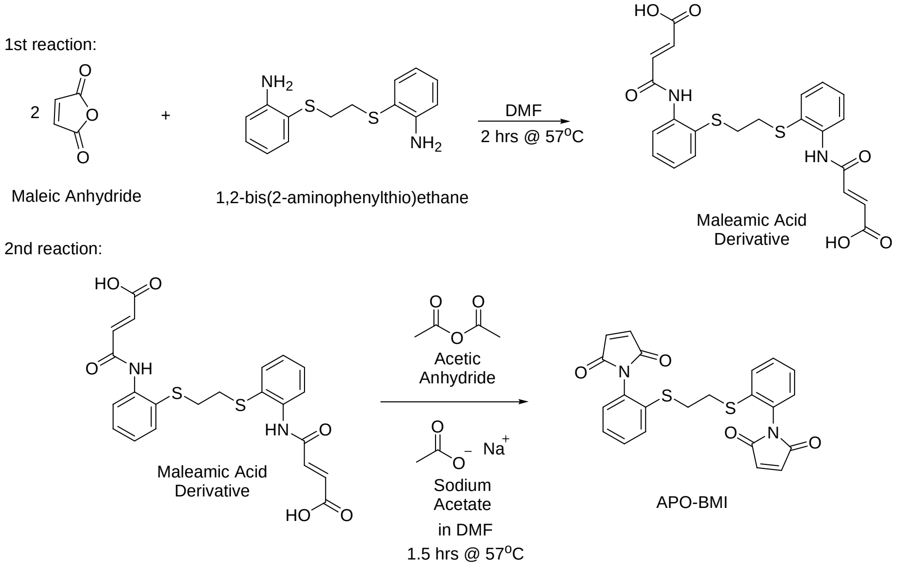


1,2-bis(2-aminophenylthio)ethane

also known as:
APOCure 601
Cyanacure (American Cyanamid)
Versalink C138 (Air Products)
APO-Link (LANL/KCP)

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

Since the material is no longer commercially available, it will be manufactured in-house at the 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.



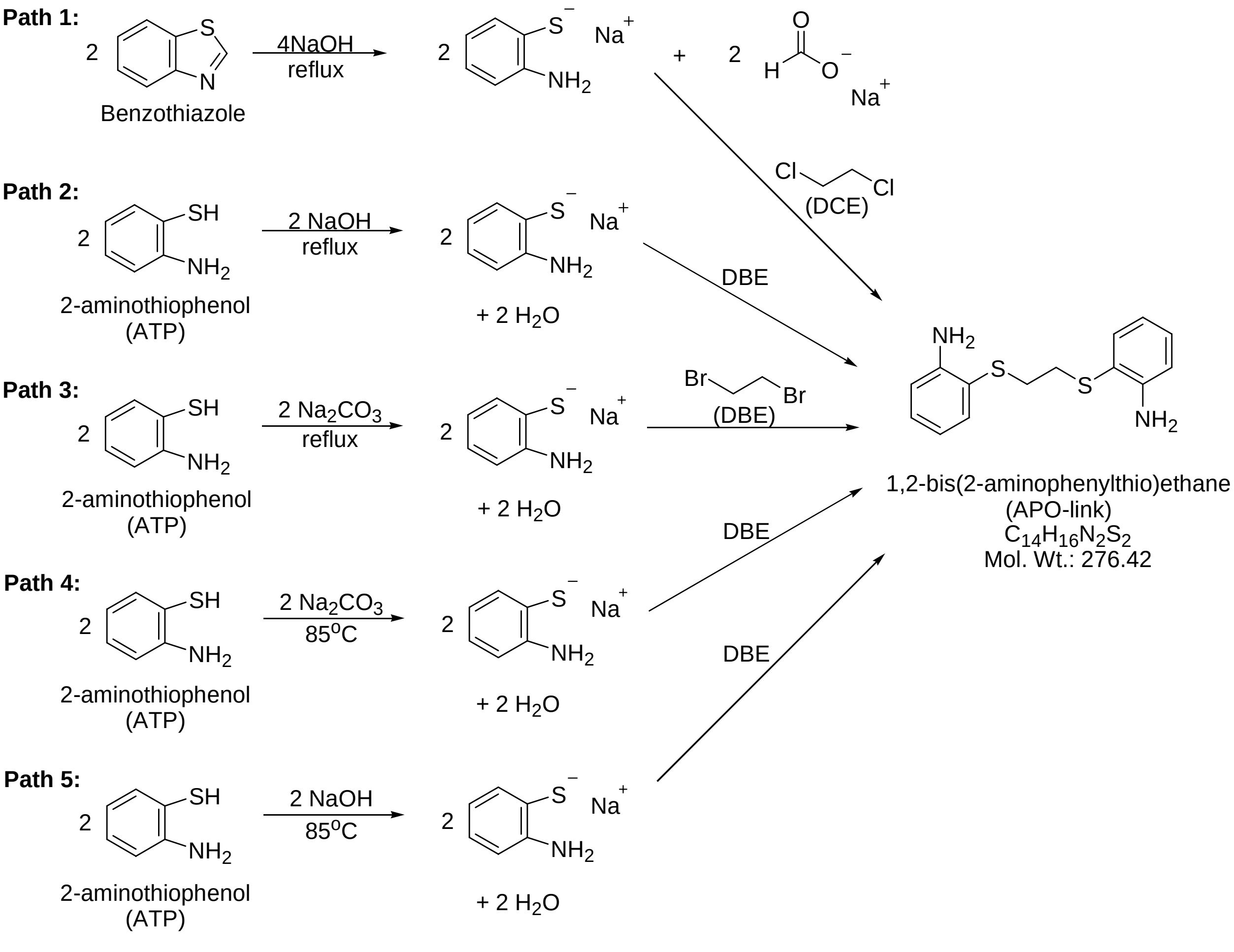
Scheme 1. Synthesis of APO-BMI resin from 1,2-bis(2-aminophenylthio)ethane (APO-Link) and maleic anhydride.

Synthesis of 1,2-bis(2-aminophenylthio)ethane (APO-Link)

The goal of the synthetic development of APO-Link was to optimize a procedure that was suitable for 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 an United States 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 drop-wise 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 toward the synthetic optimization of APO-Link. Synthesis work was completed in laboratory glassware at LANL as well as a fully instrumented 1L reaction calorimeter at KCP.



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).

Materials and Methods

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+%), ethanol (AAPER, nondenatured, Absolute 200 proof or 190 proof). All reagents were used as received without additional purification.

Characterization methods included nuclear magnetic resonance spectroscopy (NMR), Fourier transform infrared spectroscopy (FTIR), gas chromatography coupled with mass spectrometry (GCMS), gel permeation chromatography (GPC), and inductively coupled plasma spectroscopy (ICP). Additional details for each method can be found in the appendix.

General Baseline 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 deionized water was heated to reflux for 4-4.5 hours. The mixture was allowed to cool to 60-65^{o}C and dichloroethane (DCE, 0.050 mol) was added drop-wise over 20-30 minutes. The mixture was then heated to reflux for 2 hours. 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 1L reactor vessel. Benzothiazole (1.13 mol) was fed to the reactor over a period of 15 minutes. The reaction progressed for 4 hours at 116°C. Dichloroethane or dibromoethane (DCE/DBE, 0.57 mol) was then fed to the reactor over a period of 20 minutes. The reaction progressed for 2 hours at 105°C. Following work-up, the crude product was recrystallized and characterized.

General Reaction Conditions with 2-Aminothiophenol (ATP) (Path 2&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 deionized water was heated to reflux for 30 minutes. The mixture was allowed to cool to 60-65^{o}C and dibromoethane (DBE, 0.050 mol) was added drop-wise over 20-30 minutes. The mixture was then heated to reflux for 1.5-2 hours. 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 1L reactor vessel. 2-Aminothiophenol (ATP, 2 mol) was fed to the reactor over a period of 30 minutes. The reaction progressed for 30 minutes at 116°C. Dichloroethane or dibromoethane (DCE/DBE, 1 mole) was then fed to the reactor vessel over a period of 60 minutes. The reaction progressed for 1.5 hours at 105°C. Following work-up, the crude product was recrystallized and characterized.

General Reaction Conditions with 2-Aminothiophenol (Path 4&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 deionized water was heated at 80-85^oC for 30 minutes. Without additional cooling, dibromoethane (DBE, 0.050 mol) was added drop-wise over 20-30 minutes. The mixture was then heated at 80-85^oC for 1.5-2 hours. 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 1L reactor vessel. 2-Aminothiophenol (ATP, 2 mol) was fed to the reactor over a period of 30 minutes. The reaction progressed for 30 minutes at 85°C. Dichloroethane or dibromoethane (DCE/DBE, 1 mole) was then fed to the reactor vessel over a period of 60 minutes. The reaction progressed for 1.5 hours at 85°C. Following work-up, the crude product was recrystallized and characterized.

Optimization Efforts for the Production of APO-Link

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. A detailed discussion of our results can be found in the appendix.

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.

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 US 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 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 US 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. The solubility of NaOH at 20^oC is 111g/100mL water compared to the solubility of Na_2CO_3 at 20^oC is 30g/100mL water. 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^{o}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 (m.p. 50-65^{o}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 loss of the crude material while effectively removing salts. Five methods for work-up/extraction were studied during bench-scale work. Details of each method can be found in the appendix. The five methods are:

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 1L reaction calorimeter or jacketed cylindrical reactor, work-up was completed directly 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. This method of work-up was used because it was efficient and mimicked the desired full-scale method.

Recrystallization/Purification

Another processing hurdle involved purification of the crude product via recrystallization. In US 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 refs.[11-13] However, ethanol is 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 appendix. Using typical bench-scale recrystallization techniques, the purified APO-Link crystallized out 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 filtrations 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 processing and drying. 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 1st 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. *95/5 (v/v) Ethanol/Water:* Crude product is still considerably soluble in this solvent combination at room temperature.

3. *50/50 (v/v) Ethanol/Water:* 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. *80/20 (v/v) Ethanol/Water:* The crude product is largely insoluble at room temperature but dissolves in a reasonable amount of hot solvent. From the crude, the yield of the 1st recrystallized crop was improved to approximately 70% compared to only 25-35% for the 1st recrystallized crop from 100% ethanol or 95/5 (v/v) ethanol/water.

5. *Ethanol followed by drop wise addition of water:* We attempted to decrease the total solvent volume further by dissolving the crude in a minimal amount of hot ethanol and seeding the crystallization by adding water drop-wise. This method worked quite well; however, we still had the problem of "caking."

6. *Constant agitation method:* Although we achieved good recrystallized recovery and purities with the previous two methods, we still needed to get the purified material into a form that could be easily transferred and dried on a large scale. Stirring during recrystallization is contrary to conventional organic chemistry techniques. However, with this particular material and optimized solvent combination, we were able to stir the solution rapidly during cooling to yield a slurry of recrystallized APO-Link. The slurry could be transferred, filtered and dried efficiently. Both 80/20 ethanol/water by weight and by volume were used in the small-scale development. The weight percent would be used for scale-up since it is more practical to weigh large amounts of solvents. In terms of feasibility for scale-up, this 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. The recommendation was to cool the recrystallization slurry to 25°C on full-scale, which was achievable with existing equipment and resulted in 70-80% overall reaction yield.

Corrosion Study of APO-Link Synthesis

A major concern was the corrosive nature of the APO-Link reactions, especially path 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 1).

Table 1. Metal content of APO-Link samples prepared in Hastelloy Vessel. Concentration (mg/Kg) is average of triplicate analysis. nd = not detected

Sample	Ni	Mo	Cr
KCP – 04062005	86.0	37.4	nd
KCP – 05182005	136.8	8.8	nd

The existing 100-gallon reactors at KCP's Polymer Production Facility are lined with glass. Reactor A is lined with Pfaudler 3115 multi-purpose glass and reactor D is lined with DeDietrich 3009 multi-purpose 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 to 40 years. The DeDietrich 3009 glass did not show any discernable thinning under path 2 conditions, thus the lifetime was predicted to be limitless. Since our final optimization uses sodium hydroxide at 85°C (path 5), there are even less concerns over reactor corrosion and damage. Reactor D was chosen to be used 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 1st reaction, the molar heat of reaction was 43.23 kJ/mol. During the addition of dibromoethane in the 2nd phase of the reaction, the molar heat of reaction was 214.79 kJ/mol. This information is needed for full-scale production in order to assess heat removal requirements.

Addition Rate and Rinsing

Prior to scale-up, we also investigated the addition rate of dibromoethane since that portion of the reaction is much more exothermic. In VCD083, DBE was added over 60 minutes and in VCD087, DBE was added over 180 minutes. There was no significant difference in the overall yield and purity between the two reactions. Thus, a 60-minute addition time of DBE was recommended to reduce overall processing time. In VCD119, the 3rd water rinse was eliminated to see if the overall rinsing time could be reduced. The yield and purity of the recrystallized product following the 2nd rinse was quite good. Thus, it may be possible to eliminate the 3rd hot water rinse on large-scale. 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.

APO-Link Samples

Table 2 summarizes the results of bench-scale APO-Link reactions performed at LANL and KCP. The progression of the reaction paths, work-up and recrystallization methods can be seen in this table.

Table 2. Summary of Bench Scale APO-Link Reactions. Reaction scales are based on 0.10 mol benzothiazole or ATP unless otherwise noted. Crude yield percentage is based on calculated theoretical yield.

Reaction:	Condition:	Work-Up Method:	Crude Yield %:	Crude Purity %APO-Link (GCMS)	Crude Purity %APO-Link (GPC)	Rextal Method:	GCMS %APO-Link	GPC %APO-Link
IVCD074	Path 1	1	56%	55.35	--	1	96.23	--
IVCD082-1	Path 1	2	80%	57.90	--	1	94.57	--
IVCD082-2	Path 1	2	80%	57.90	--	3	98.44	--
IVCD087	Path 1	3	60%	58.63	--	2	87.40	--
IVCD091	Path 1	2	79%	51.54	--	2	90.57	--
IVCD100	Path 1 (w/DBE)	4	90%	63.24	--	4	87.56	--
050406 (2.0 mol Benzothiazole)	Path 1	5	*	--	74.0	5	--	96.00
050719 (2.0 mol Benzothiazole)	Path 1	5	70%	--	87.0	5	--	93.30
IVCD103	Path 2	4	89%	63.24	--	4	85.82	--
IVCD112-1	Path 2	4	89%	62.12	--	4	89.12	--
IVCD112-1	Path 2	4	89%	62.12	--	5	93.70	--
050927 (2.0 mol ATP)	Path 2	5	93%	--	89.0	6	--	92.30
060116 (6.0 mol ATP)	Path 2	5	90%	--	84.0	6	--	93.82
IVCD120	Path 3	4	92%	60.55	--	5	98.38	--
IVCD117	Path 3	4	93%	61.55	--	5	97.21	--
IVCD125	Path 4	4	93%	59.21	--	**5	71.62	--
IVCD130	Path 4 (w/DCE)	4	83%	58.36	--	5	96.56	--
IVCD134 (1.0 mol ATP)	Path 4	4	92%	68.85	--	5	97.25	94.6
IVCD142/APO121605-1 (2.0 mol ATP)	Path 5 (DBE addn. 45 mins.)	5	88%	61.78	80.0	**5	98.07	97.22
IVCD142/APO121605-2 (2.0 mol ATP)	Path 5 (DBE addn. 45 mins.)	5	88%	61.78	80.0	6	97.77	97.95
060406 (2.0 mol ATP)	Path 5	5	*	--	88.0	6	99.3	97.80
VCD083 (2.0 mol ATP)	Path 5 (DBE addn. 60 mins.)	5	*	90.95	--	6	98.04	97.42
VCD087 (2.0 mol ATP)	Path 5 (DBE addn.	5	*	91.34	--	6	96.76	95.43

	180 mins.)							
VCD119 (2.0 mol ATP)	Path 5 (DBE addn. 60 mins. & rextal after 2nd rinse)	5	*	91.54	--	6	98.04	95.79

*Total crude product was not isolated and dried.

**After drop wise addition of water, the recrystallization solution was stirred during cooling.

APO-Link Impurities

Both GCMS and NMR spectroscopy were used to characterize the starting materials (see appendix), crude products, recrystallized products and organic material remaining in aqueous extracts. For reactions involving the hydrolysis of benzothiazole, NMR of the crude product showed evidence of unreacted benzothiazole, 2-aminophenyldisulfide, and a thiazine derivative in addition to other impurities in smaller amounts. Figure 4 shows ^{1}H NMR spectra of commercially available 2-aminophenyldisulfide (reaction by-product) and benzothiazole compared to the spectra of the crude APO-Link product from IVCD074. Only the ^{1}H NMR spectrum of IVCD074 is shown; however, the crude product spectra are similar for all path 1 reactions with benzothiazole. Figure 5 more clearly illustrates the spectral signature of APO-Link and impurities in the crude material.

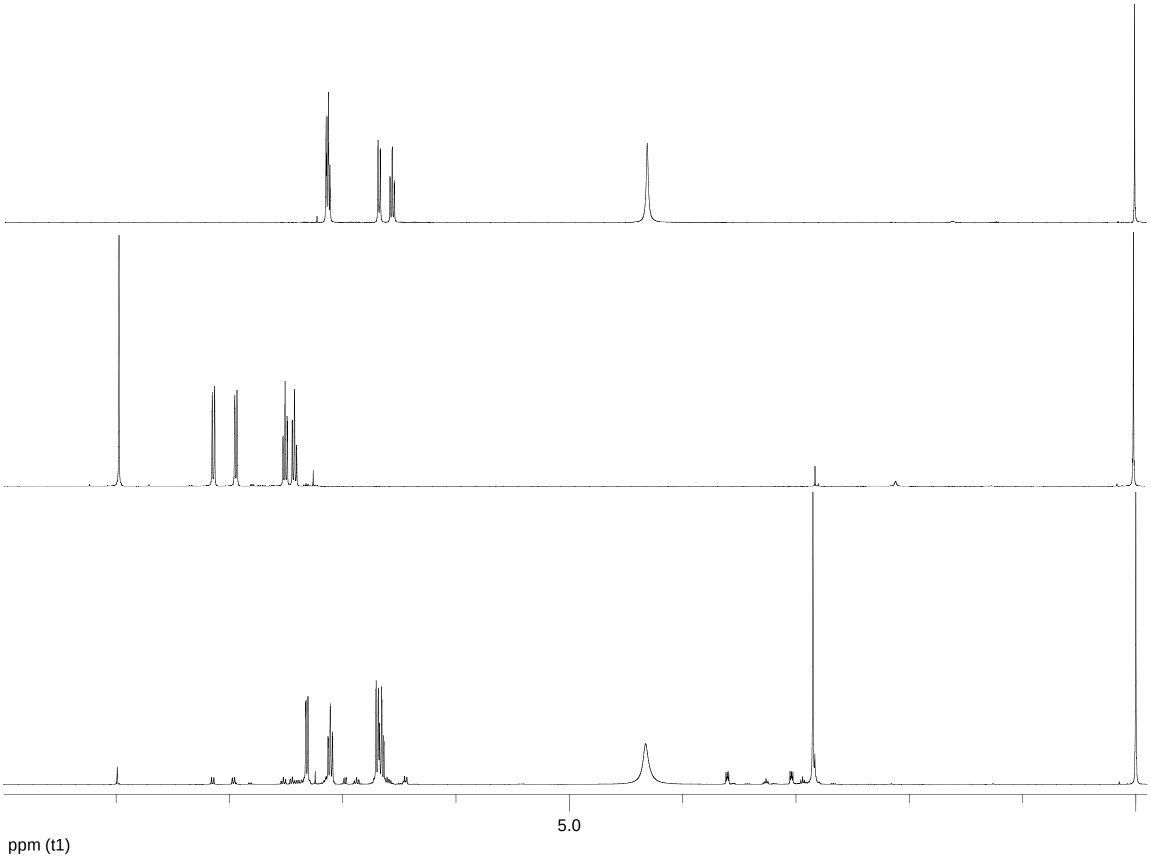


Figure 4. ^{1}H NMR spectra of commercially available 2-aminophenyldisulfide and benzothiazole compared to the crude APO-Link product from IVCD074.

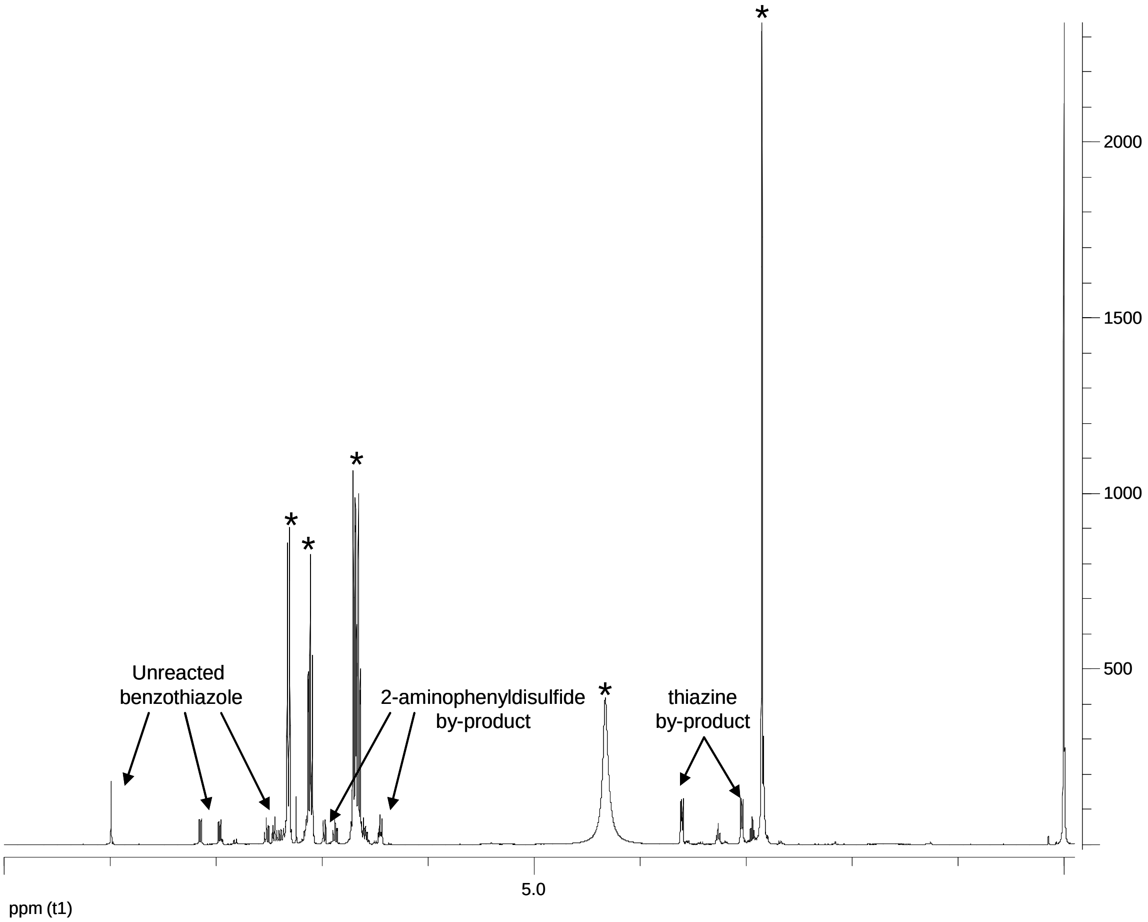
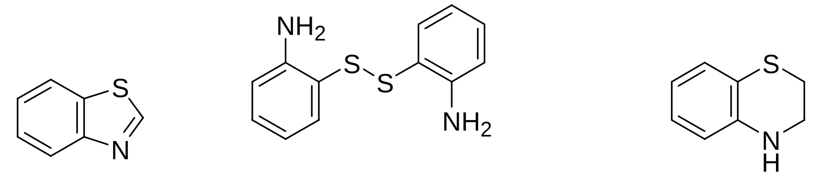


Figure 5. ^{1}H NMR of crude APO-Link product from IVCD074 and identification of impurities. *denotes peaks from APO-Link.

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 Based on NMR and GCMS.



Benzothiazole
C_7H_5NS
Mol. Wt.: 135.19

2-aminophenyldisulfide
$C_{12}H_{12}N_2S_2$
Mol. Wt.: 248.37

3,4-Dihydro-2*H*-benzo[1,4]thiazine
C_8H_9NS
Mol. Wt.: 151.23

Figure 6. Impurities in crude APO-Link product from reaction path 1.

The crude materials from reactions with 2-aminothiophenol (paths 2-5) were also examined with NMR and GCMS. By ^{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 based on NMR and GCMS.

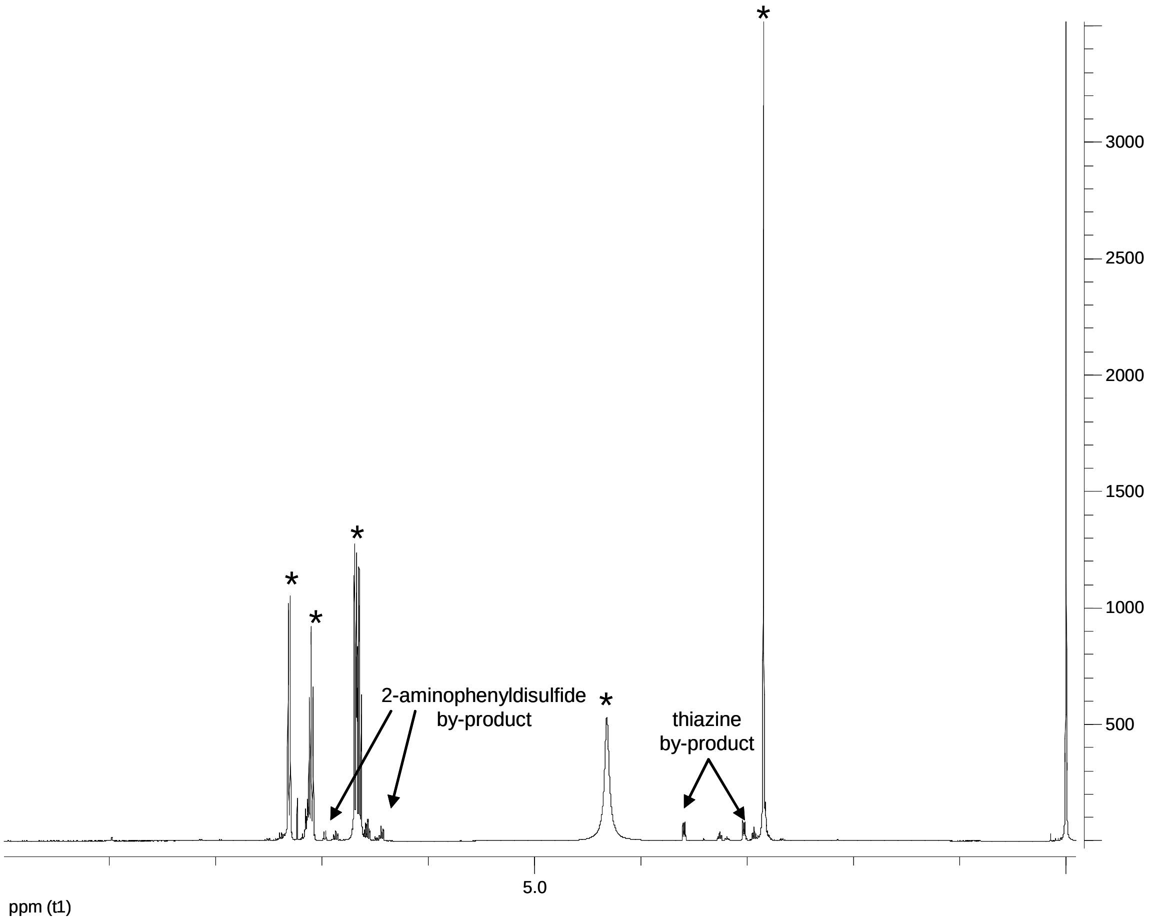
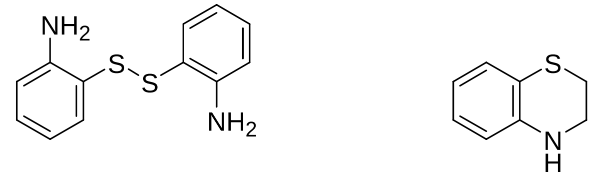


Figure 7. ^{1}H NMR of crude APO-Link product from IVCD103 and identification of impurities. *denotes peaks from APO-Link.



2-aminophenyldisulfide
$C_{12}H_{12}N_2S_2$
Mol. Wt.: 248.37

3,4-Dihydro-2*H*-benzo[1,4]thiazine
C_8H_9NS
Mol. Wt.: 151.23

Figure 8. Impurities in crude APO-Link product from reaction path 2 (IVCD103).

The disulfide and thiazine derivatives were common impurities in both the hydrolysis of benzothiazole (path 1) and deprotonation of 2-aminothiophenol (paths 2-5). NMR and GCMS showed evidence of these impurities in Cyanacure and Versalink as well. Residual benzothiazole was also observed in APO-link samples from path 1.

Final Recommendations

Recommended Procedure for Scale-Up

Based on our work, the recommended reaction conditions for scale-up consist of the deprotonation with 2-aminothiophenol with sodium hydroxide at 80-85°C followed by addition of dibromoethane. The recommended method for work-up involves rinsing the crude product multiple times with hot water to keep the crude product melted. The organic and aqueous phases can be cleanly separated by draining the reactor. The recommended method for recrystallization uses an 80/20 (w/w) ethanol/water solution. The material is dissolved in the ethanol/water and agitated rapidly while the solution cools to room temperature. A thick slurry of finely divided, purified APO-Link results from this recrystallization process. After drying, this procedure consistently gives 75-80% overall yield of purified product on small scale.

Detailed Optimized Procedure

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 1L, 4-neck cylindrical jacketed reactor with bottom outlet. Sodium hydroxide (2.02 mol, Acros Organics 98%, 82.42g) 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 minutes while maintaining the temperature at 85±5°C.

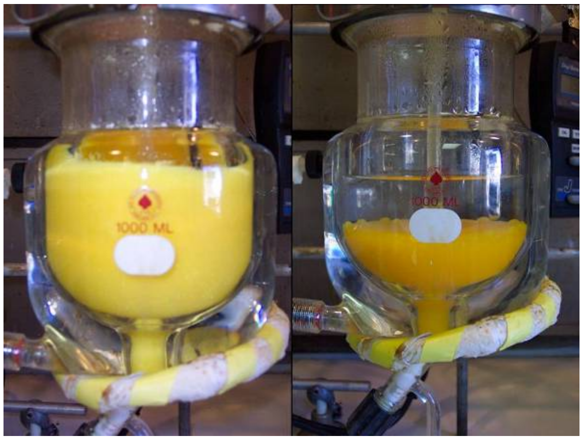
Figure 9. A) During addition of ATP. B) Addition of ATP is complete.

Following the addition of ATP, the mixture was allowed to stir at 85±5°C for 30 minutes. 1,2-dibromoethane (1.0 mol, Aldrich 99%, 187.74 g = 87.04 mL) was transferred to a graduated pressure-equalizing addition funnel. Dibromoethane (DBE) was added to the reaction mixture over 60 minutes 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 minutes.

A B

Figure 10. A) Addition of DBE is complete. B) Initial phase separation with organic layer on top.

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 hot deionized water was added to the reactor and the mixture was agitated for approximately 15 minutes (1st rinse). Agitation was stopped and the phases were allowed to separate for 5-10 minutes. The organic crude material (now bottom layer) was quickly removed 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.



A B

Figure 11. A) 1st rinse. B) Phase separation following 1st rinse with organic layer on bottom.

For recrystallization, approximately 500 mL 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 minutes to ensure complete dissolution. The temperature of the recirculating water in the reactor jacket was adjusted to 20.0^{o}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 crystallization so that the purified product would not "cake out" on the reactor.

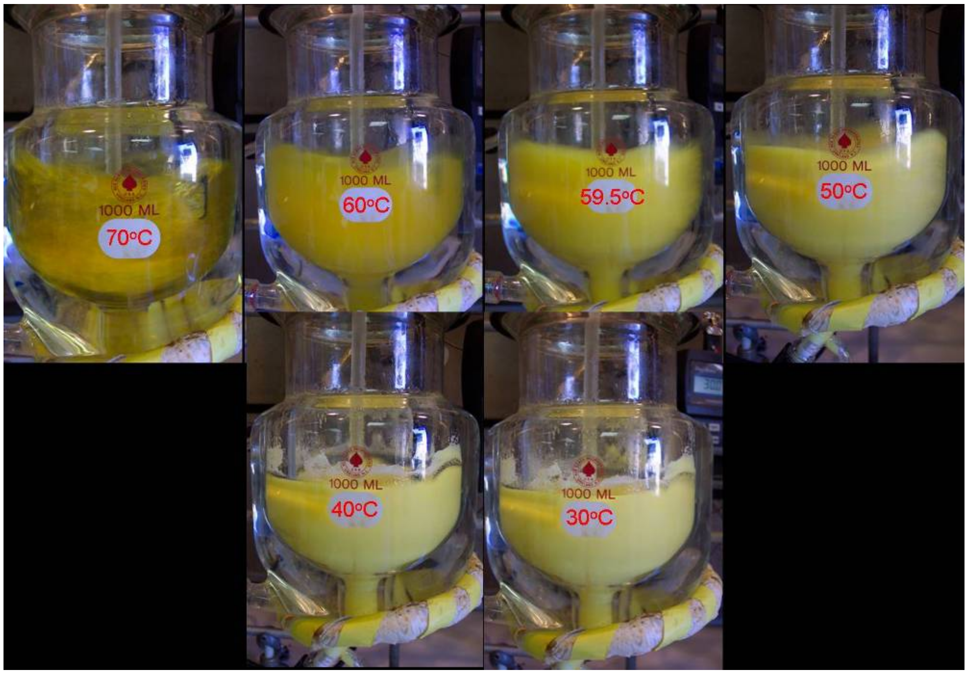


Figure 12. Temperature of slurry as recrystallization proceeds.

When the recrystallization solution reached approximately 60^{o}C, finely dispersed solid began to come out of solution. At approximately 40^{o}C, the mixture was a relatively thick slurry of fine, light yellow solid. The slurry was cooled to approximately 20-25^{o}C 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 chilled (approximately 5^{o}C) 80/20 (w/w) ethanol/water. The material was transferred to large dish and dried under reduced pressure at 45^{o}C for 48 hours. The final dried material was a powdery, light yellow solid.

Figure 13. Purified APO-Link material from optimized bench-scale synthesis.

Conclusion

The recommended procedure for scale-up 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 GCMS. Our work has provided valuable characterization information for the material specification along with a scalable procedure for the APO-Link processing specification. 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 lab and pilot-plant to develop a practical synthetic process for scale-up.

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Appendix I

Analytical Methods

Nuclear Magnetic Resonance Spectroscopy (NMR)

Samples were prepared by dissolving approximately 50 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 ^1H and 100.62 MHz for ^{13}C). For ^1H, 16 scans were collected and for ^{13}C, at least 176 scans were collected. All spectra were referenced against TMS at 0 ppm.

Fourier Transform Infrared Spectroscopy (FTIR)

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.

Gas Chromatography coupled with Mass Spectrometry (GCMS)

Samples were prepared by dissolving 0.20 g sample in 9.7 g acetonitrile with 0.1 g of a 1% diglyme internal standard solution in acetonitrile. An Agilent 5890 Gas chromatograph with a 5971 Mass spectrometer were used. The separation of APO-Link samples results in a total ion chromatograph (TIC). The peaks are identified using established GC peak retention times for the conditions of this analysis and comparison to mass spectra. The GCMS column was a Restek Rtx-5 30m x 0.25mm ID x 0.25 µm film. The injection port temperature was 250ºC. The sample was injected with split injection mode consisting of a 1 uL injection with 8:1 split flow ratio. The oven temperature was 50ºC with a ramp of 10ºC/min to 280ºC followed by an isotherm at 280ºC for 20 minutes. The MS transfer temperature was 280ºC. The quantitation is a relative quantitative method based on calculating the area of all the peaks, summing all the areas and then dividing the area of each peak by the total area of all the peaks. This gives a relative concentration and requires no standards. Using these conditions, the retention time of APO-Link was approximately 26.8 minutes.

Gel Permeation Chromatography (GPC)

Samples were prepared by dissolving approximately 20 mg sample in 10mL tetrahydrofuran (THF stabilized with BHT). Stabilized THF was used as the mobile phase with three Waters high resolution HR0.5 columns arranged in-line. 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 ~60Å pore size. As with GCMS, the GPC quantization with is a relative method based on calculating the area of all the peaks, summing all the areas and then dividing the area of each peak by the total area of all the peaks.

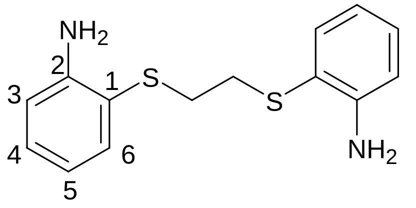
Inductively Coupled Plasma Spectroscopy (ICP)

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 hours. The sample was filtered first through 5-micrometer syringe filter and then filtered a second time through 0.45 micron 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 mult-element reference standard. A non-quantitative 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.

Appendix II

Characterization and Comparison of Cyanacure and Versalink

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." The ^1H and ^{13}C NMR spectra of Cyanacure and Versalink are consistent with an aromatic diamine. The spectra are identical and show a high level of purity for both materials. The bond labels for NMR assignment are depicted in figure AII-1.



1,2-bis(2-aminophenylthio)ethane

Figure AII-1. Bond labels for ^1H and ^{13}C NMR assignment of 1,2-bis(2-aminophenylthio)ethane samples.

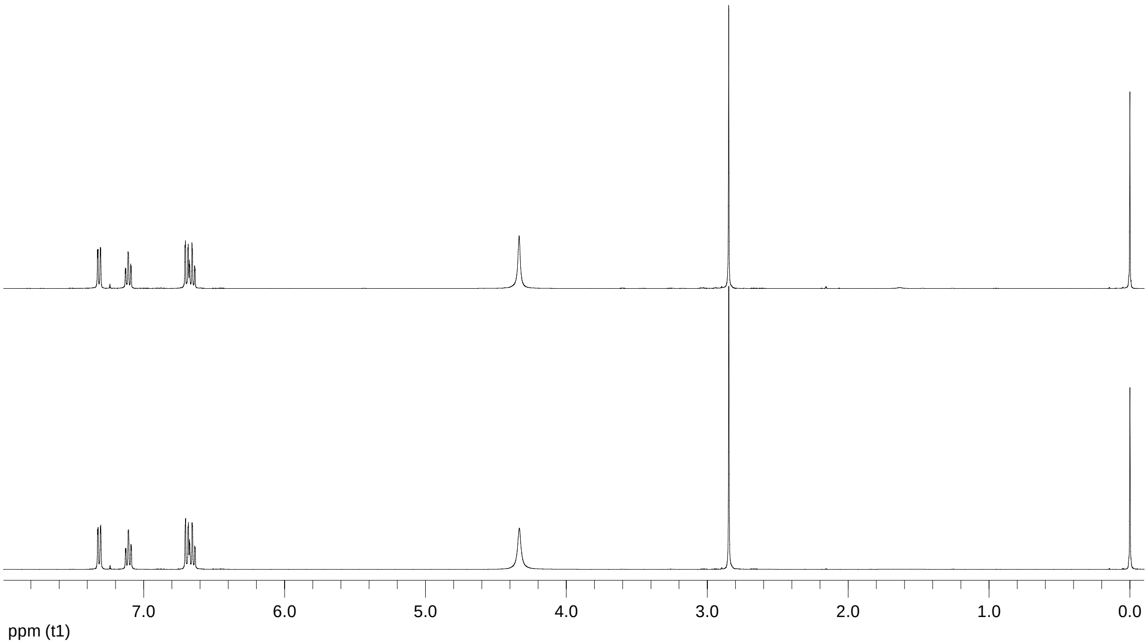


Figure AII-2. ^1H NMR of Cyanacure and Versalink in $CDCl_3$ with 1%(v/v) TMS as a reference.

Table AII-1. Peak assignments for ^{1}H NMR of Cyanacure and Versalink in $CDCl_3$.

δ (ppm relative to TMS):	**Assignment:**
2.85 (s)	$-CH_2-$
4.33 (s), broad	$-NH_2$
6.63, 6.64, 6.66, 6.67, 6.68, 6.70 (mult.)	Aromatic H at positions 4, 5
7.09, 7.11, 7.13	Aromatic H at position 3
7.30, 7.31, 7.32, 7.33 (dd)	Aromatic H at position 6

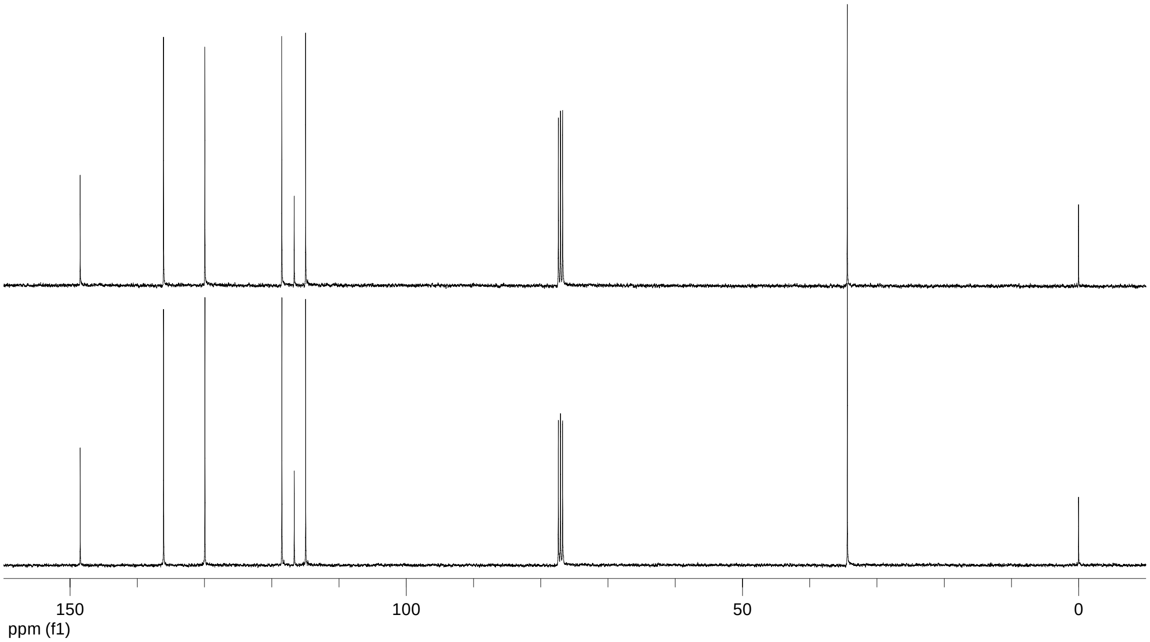


Figure AII-3. ^{13}C NMR of Cyanacure and Versalink in $CDCl_3$ with 1%(v/v) TMS as a reference.

Additional 1D and 2D NMR experiments were conducted to verify proton and carbon assignments. Figure AII-4 shows ^{13}C NMR conducted with typical proton decoupled carbon pulse sequence (top) and DEPT135 pulse sequence (bottom). Using a DEPT135 pulse sequence, the quaternary carbon atoms at positions 1 and 2 do not yield peaks. The chloroform solvent peaks do not appear as well. This pulse sequence leads to a negative peak for the APO-Link -CH_2- carbons. The peak assignments for the aromatic CH carbons were verified using a 2D HETCOR experiment that correlates the ^{1}H-^{13}C interactions in the molecule. Figure AII-5 shows the ^{1}H-^{13}C correlation map resulting from the 2D HETCOR experiment. The top axis shows the DEPT ^{13}C NMR and the side axis shows the ^{1}H NMR associated with carbon-bonded protons (-NH_2 protons do not appear). The spectrum map illustrates which protons and carbons interact, thus carbon and proton assignments can be confirmed.

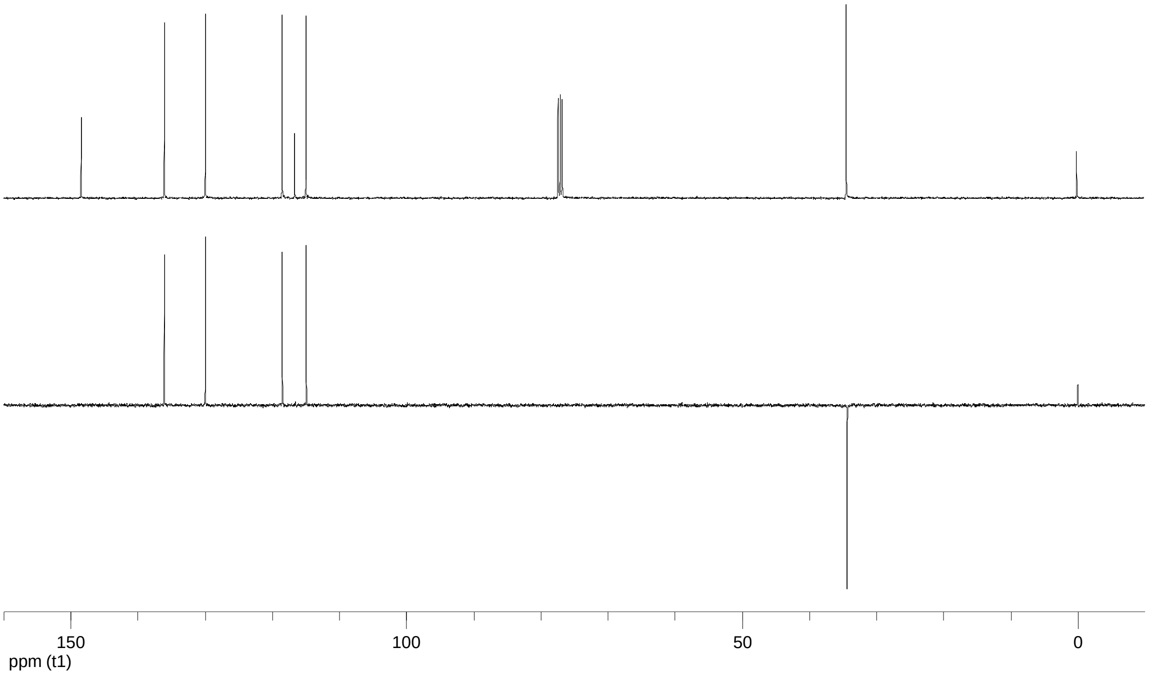


Figure AII-4. Comparison of ^{13}C NMR with proton decoupling (top) and DEPT135 (bottom) pulse sequences. (-10 to 160 ppm)

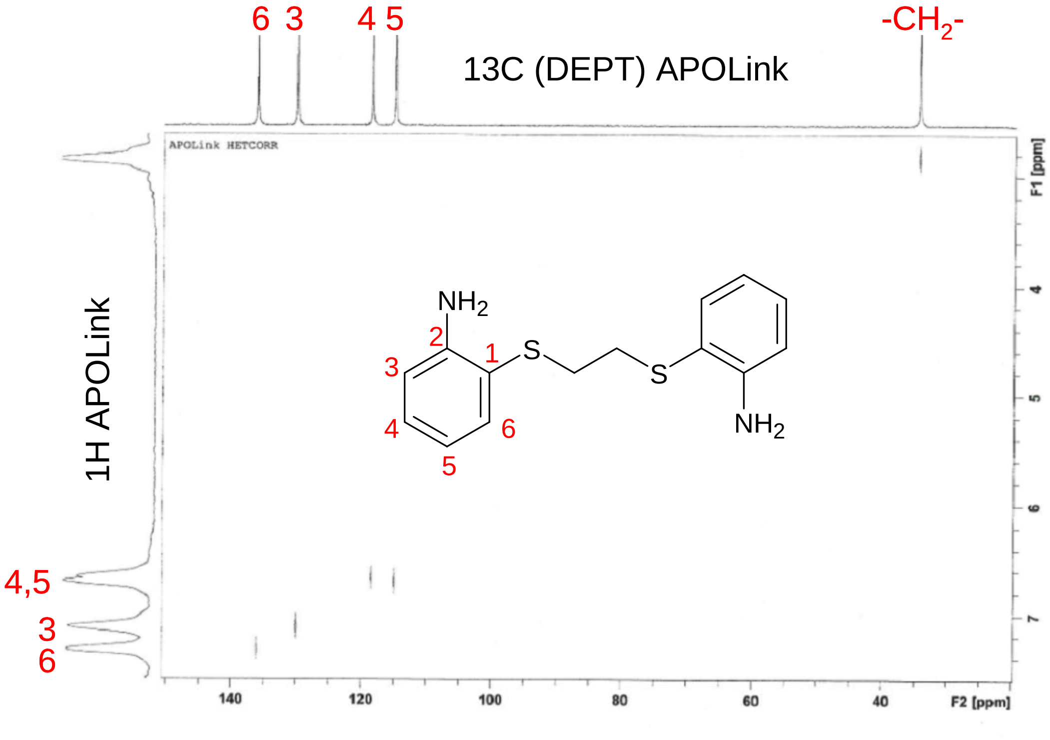


Figure AII-5. 2D HETCOR showing DEPT ^{13}C NMR (top) ^{1}H NMR associated with carbon-bonded protons (side)

The final peak assignments for proton-decoupled ^{13}C NMR are listed in table AII-2.

Table AII-2. Peak assignments for ^{13}C NMR of Cyanacure and Versalink in $CDCl_3$.

Peaks (ppm relative to TMS):	**Assignment:**
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

The FT-IR spectra of Cyanacure and Versalink are also consistent with an aromatic diamine. The spectra both show N-H stretching associated with the primary amine, aromatic and aliphatic C-H stretching and deformations associated with the aromatic ring and $-CH_2-$ linkage.

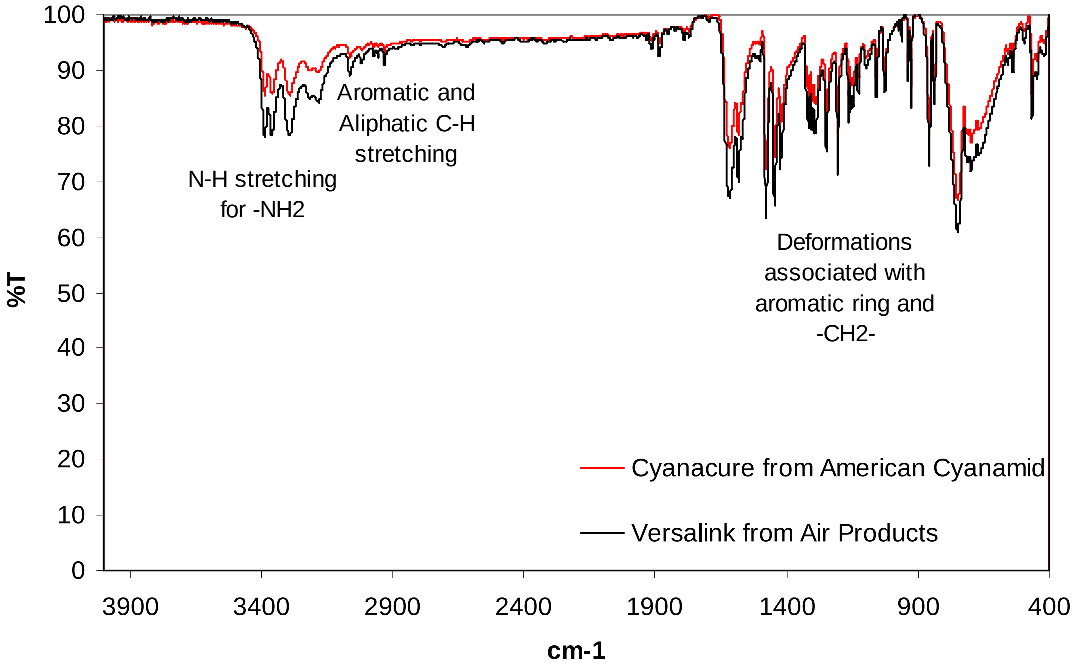


Figure AII-6. FTIR spectra from 4000-400 cm^{-1} of Cyanacure and Versalink samples prepared in KBr pellet form. Residual background peaks associated with CO_2 (2360, 2340cm^{-1}) were removed from the spectra for clarity.

The melting point of each sample was measured in a glass capillary using a Melt-Temp melting point apparatus. The reported melting point values for 1,2-bis(2-aminophenylthio)ethane are 72-73°C[11], 78°C[12], and 76°C[13]. In this work, the measured melting range of Cyanacure was 71-73°C and Versalink was 72-74°C.

Table AII-3. Purity values of Cyanacure and Versalink.

Sample:	GCMS %APO-Link	GPC %APO-Link
Cyanacure (American Cyanamid)	86.73	97.11
Versalink (Air Products)	92.61	98.08

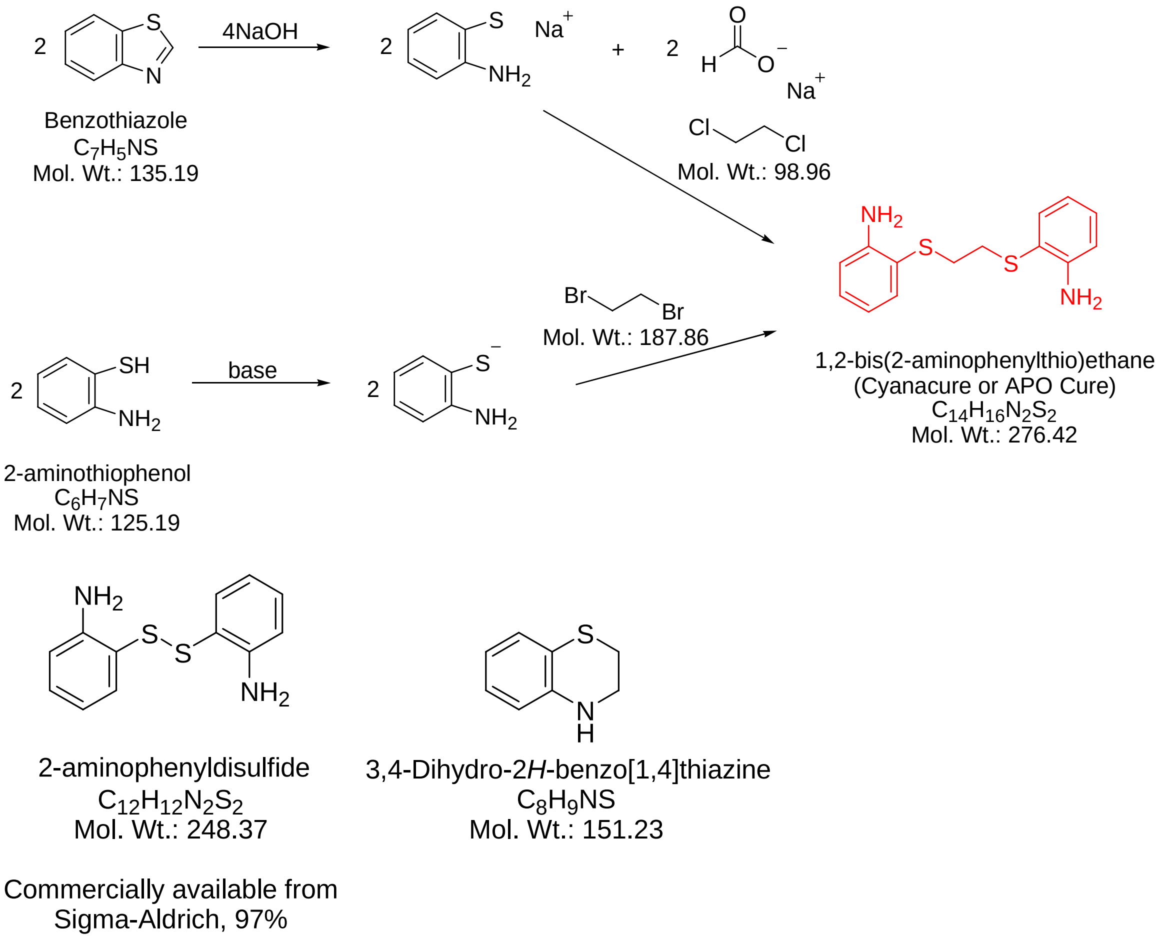
ICP analysis of Cyanacure and Versalink were also conducted and the samples showed no detectable amounts of chromium, nickel, iron or molybdenum (elements common in nickel alloy reactors). A survey scan of 66 additional metals was conducted on both Cyanacure and Versalink. Aluminum and zinc were identified in both samples at approximately 50 and 25 mg/Kg respectively. Boron, carbon, magnesium and silicon were also present at very low levels.

Table AII-4. Metal content of Cyanacure and Versalink. Concentration in average of triplicate analysis. nd = not detected

Sample	Ni (mg/Kg)	Mo (mg/Kg)	Cr (mg/Kg)	Fe (mg/Kg)	Al (mg/Kg)	Zn (mg/Kg)
Cyanacure (American Cyanamid)	nd	nd	nd	nd	50	25
Versalink (Air Products)	nd	nd	nd	nd	50	25

Appendix III

NMR Analysis of Starting Materials and Commercially Available Disulfide By-Product



Scheme AIII-1. Synthetic routes to 1,2-bis(2-aminophenylthio)ethane or APO-Link. One reaction by-product is commercially available 2-aminophenyldisulfide.

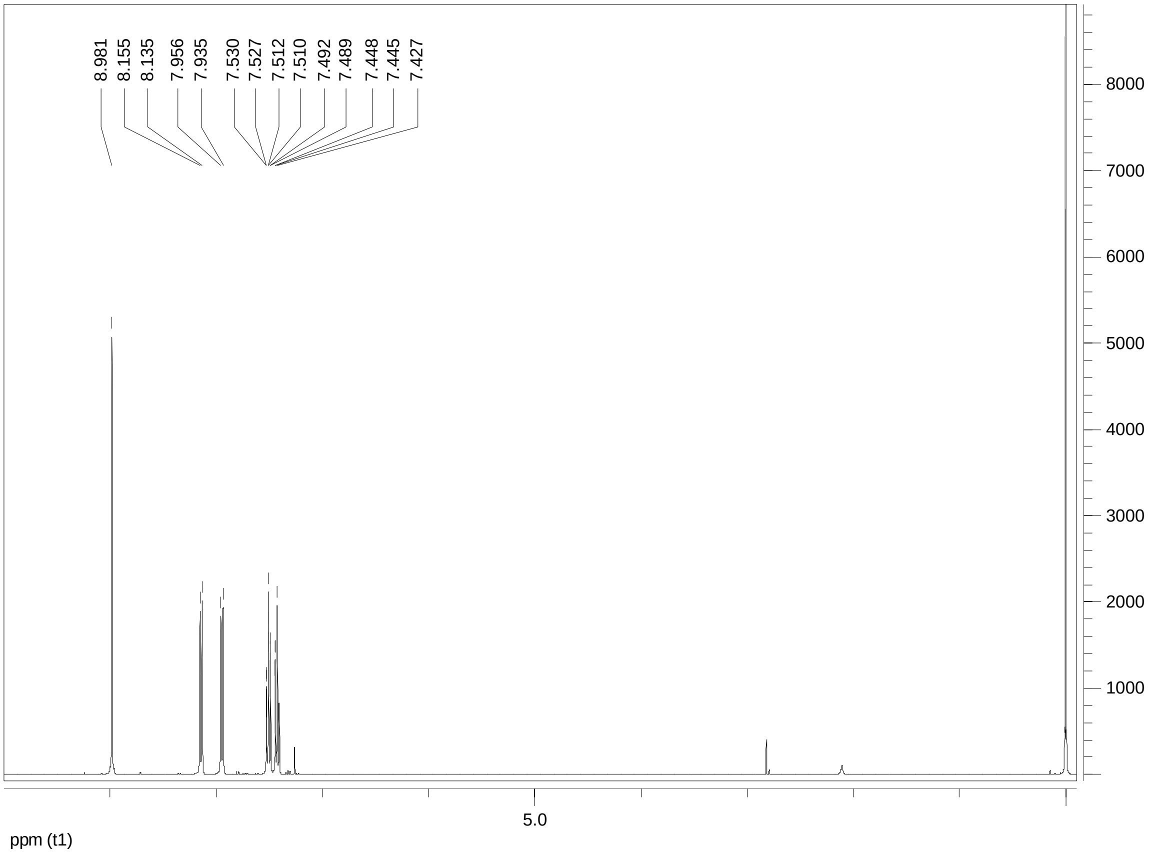


Figure AIII-1. ^{1}H NMR spectra of benzothiazole (Aldrich, 96%).

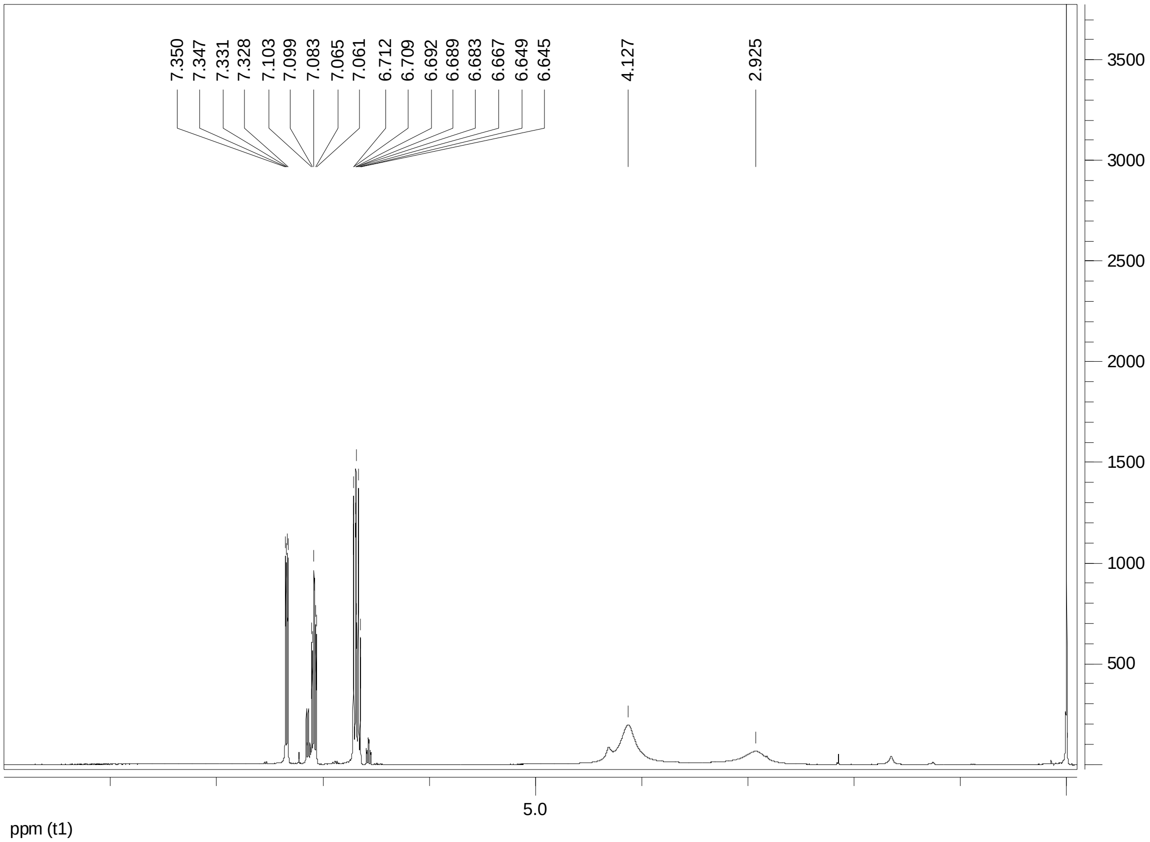


Figure AIII-2. ^{1}H NMR spectra of 2-aminothiophenol (Aldrich, 99%).

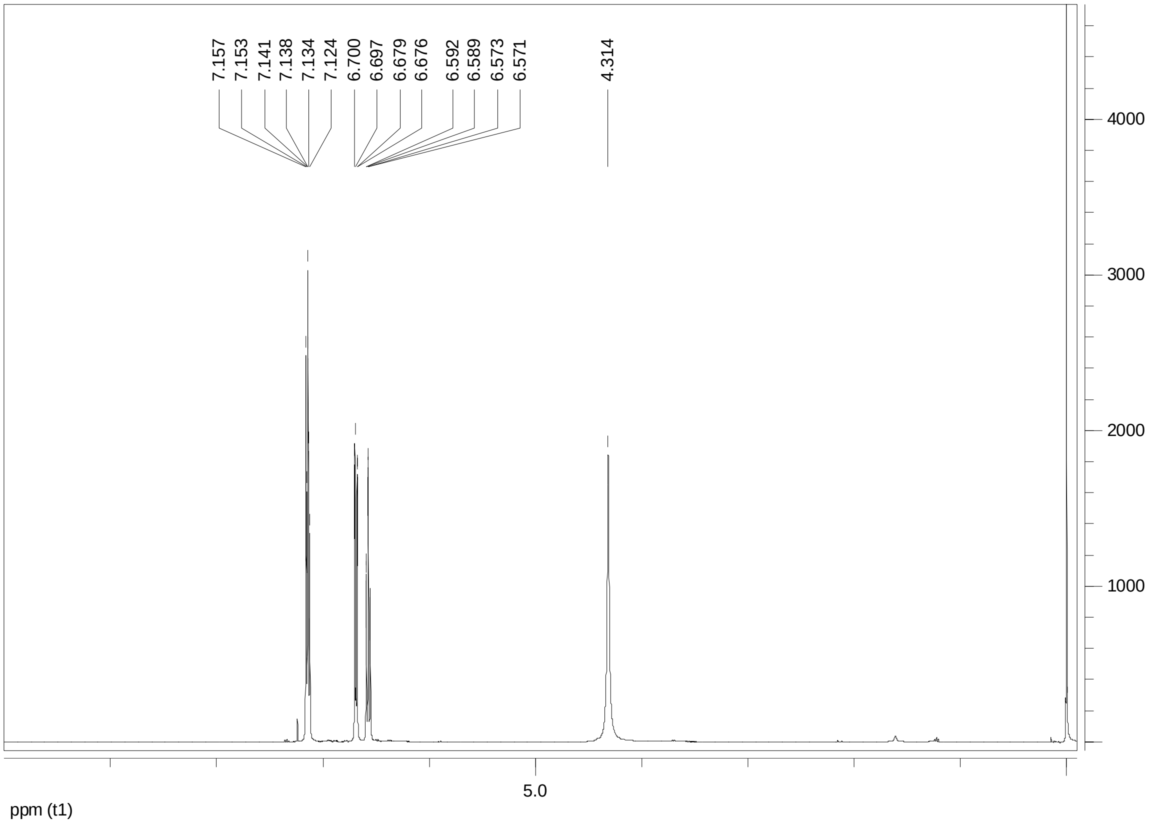


Figure AIII-3. ^{1}H NMR spectra of 2-aminophenyldisulfide (Aldrich, 99%).

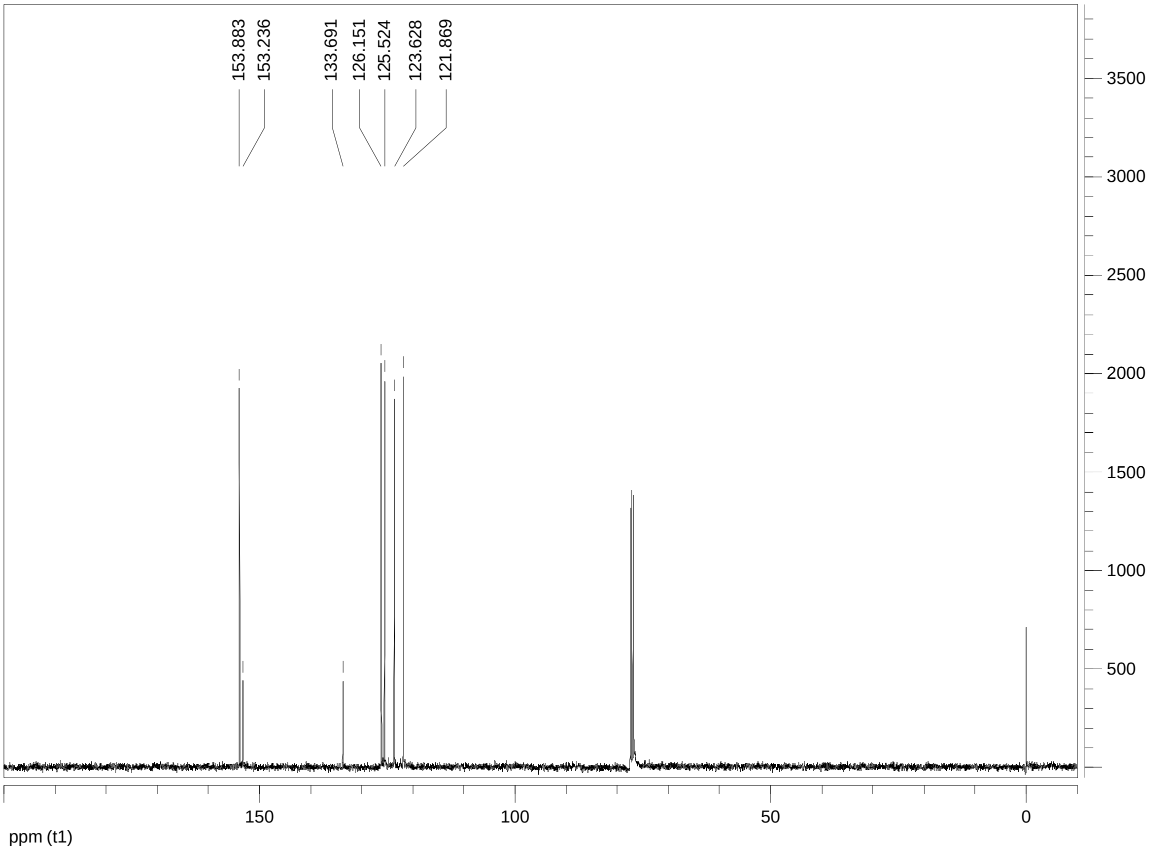


Figure AIII-4. ^{13}C NMR spectra of benzothiazole (Aldrich, 96%).

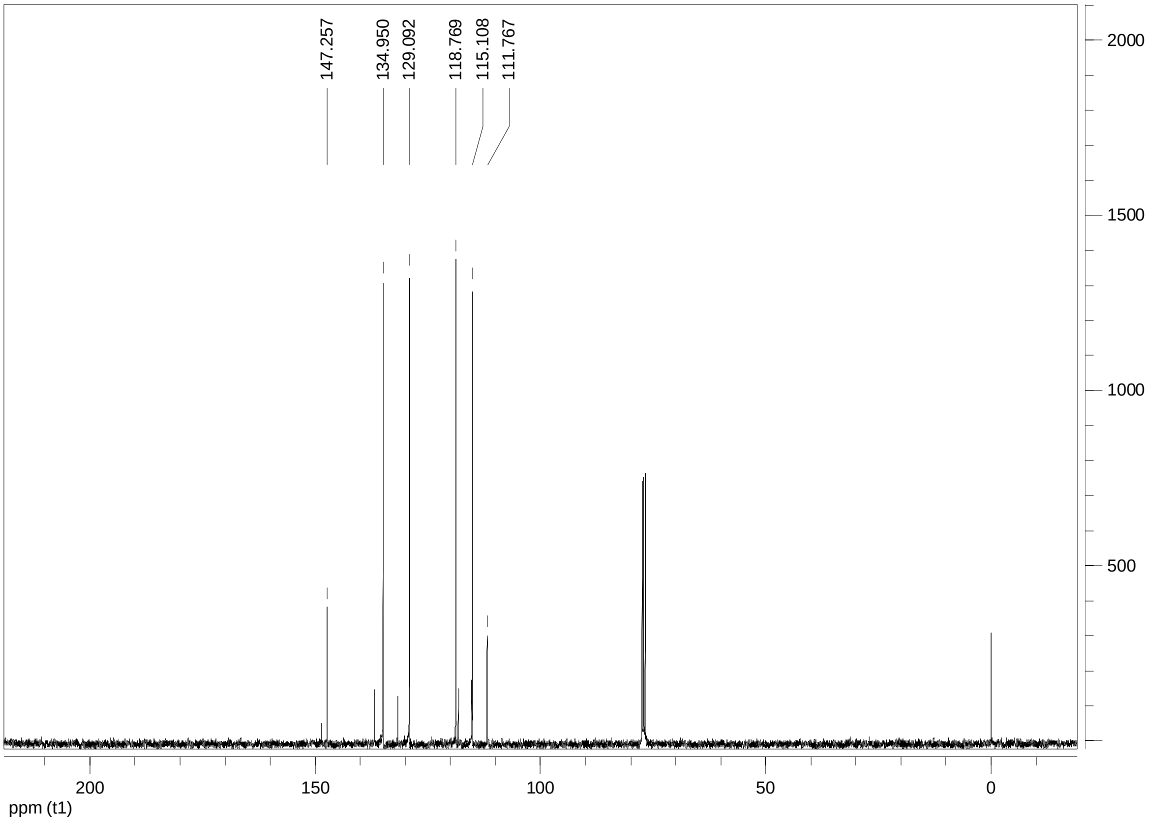


Figure AIII-5. ^{13}C NMR spectra of 2-aminothiophenol (Aldrich, 99%).

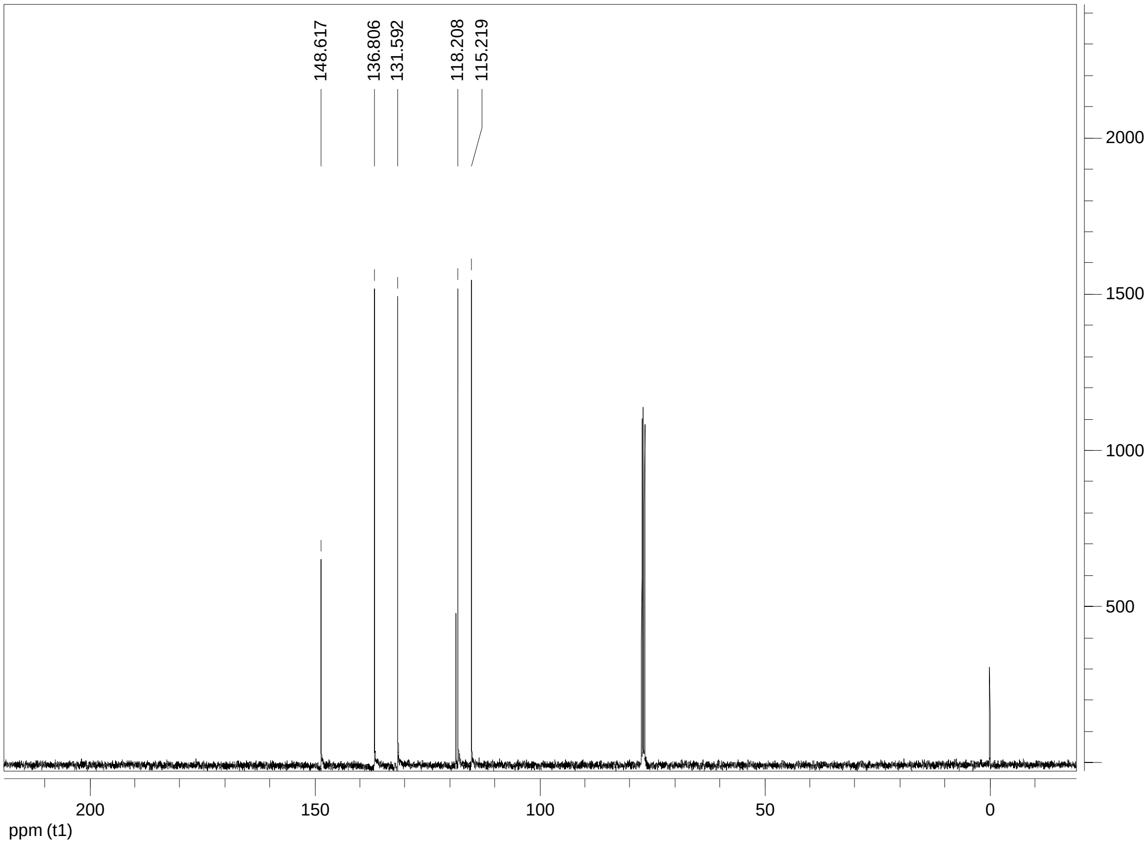


Figure AIII-6. ^{13}C NMR spectra of 2-aminophenyldisulfide (Aldrich, 99%).

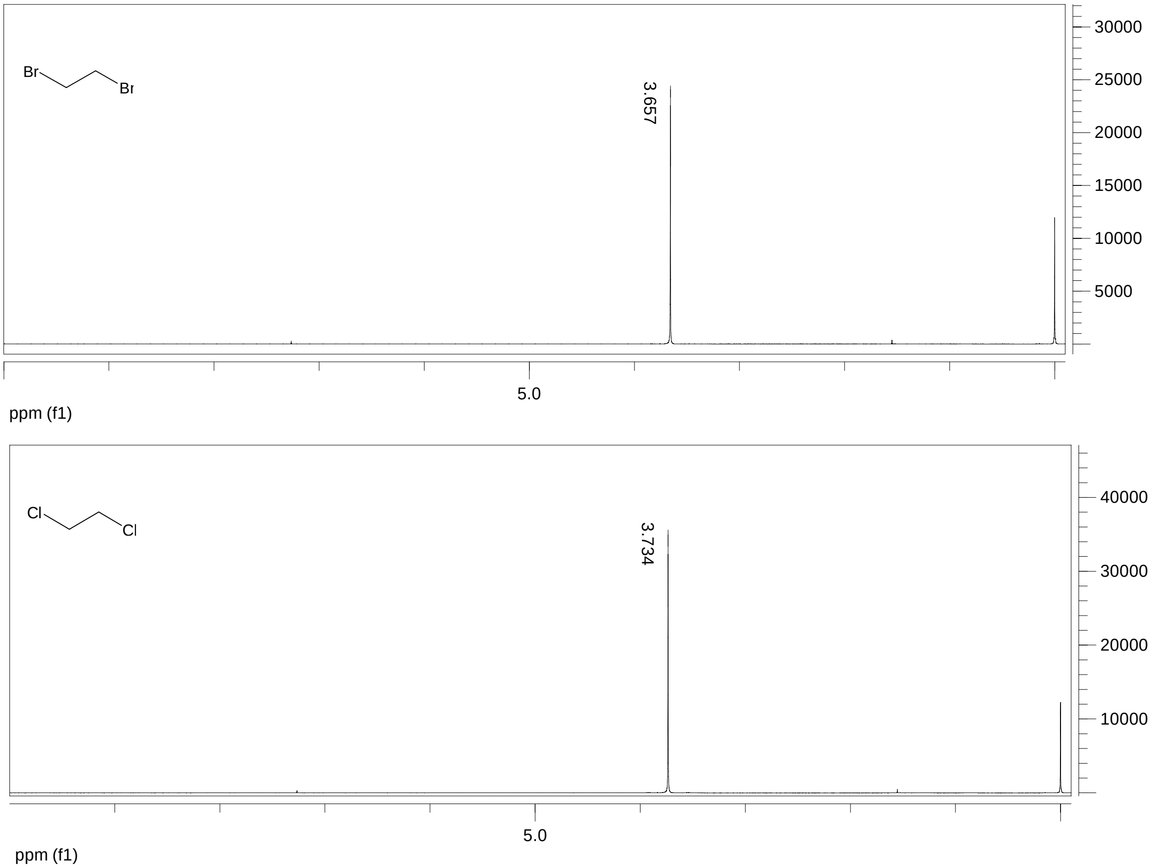


Figure AIII-7. ^{1}H NMR spectra of dibromoethane and dichloroethane.

Appendix IV

Work-up/Extraction Methods

1. *Boiling water extraction in separatory funnel.* This method was used in the original patent procedure and relies on keeping the crude product melted with boiling water while transferring the material to a separatory funnel and extracting the water-soluble salts.[10] This method is extremely messy and terribly inefficient. It is impossible to keep the crude product melted during the extraction, thus, the separatory funnel continually clogged. Due to the waxy consistency of the crude, it is impractical to consider transferring the material to a secondary vessel for extraction on large scale. Pipe clogging would likely occur.
2. *Organic/aqueous extraction with methyl ethyl ketone (MEK) and water.* Typically, salts are separated from organic material using a standard organic solvent/water extraction in a separatory funnel. MEK was selected because it is a suitable solvent for use in the Polymer Production Facility at KCP and it is immiscible with highly ionic aqueous solutions. This method seemed to improve the crude recovery compared to the boiling water extraction using a separatory funnel. However, on large scale an additional day of work-up and drying would be required and cycle time would be negatively impacted.
3. *Water extraction at room temperature.* Room temperature water was added to the hot reaction and the mixture was stirred rapidly as it cooled down. The water was decanted off and the crude product was dried. This method worked well, but, salt is likely to still be present in the crude product due to inefficient rinsing.
4. *Repeat extraction and cooling.* Room temperature water was added to the hot reaction and the mixture was stirred rapidly as it cooled down. The water was decanted off, leaving the waxy crude product. Boiling water was added to the crude product to re-melt it and the mixture was stirred rapidly as it cooled to room temperature. This process was repeated to give a total of 3 rinses. The water was decanted off and the crude product was dried. This method efficiently removed salts and resulted in approximately 90% crude product yield, however, it is not practical to cycle between molten and solidified crude on large scale. This method was simply useful for very small scale development reactions (0.10 moles benzothiazole or ATP) where a jacketed reactor with bottom drain was not available.
5. *Hot water extraction in reactor with drain.* For reactions performed in the 1L reaction calorimeter, work-up was completed directly in the reaction calorimeter because a bottom outlet drain was available. When the second reaction was completed, the layers were allowed to separate while the reactor 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 reaction calorimeter for the rinsing step. Following separation, the organic crude material (now bottom layer) was quickly drained from the reactor and then returned after the aqueous portion was drained. This process was repeated to give a total of 3 rinses. This method of work-up was used because it was efficient and mimicked the desired full-scale method.

Appendix V

Solubility of Crude APO-Link Product and Recrystallization Information

Table AV-1. Solubility characteristics of cyanacure product from IVCD082. 5 mL of solvent was added to 100 mg of material. The solubility characteristics were observed at room temperature (23-24°C) unless otherwise noted.

Solvent:	**Solubility**
Acetone	Completely soluble
2-butanone (MEK)	Completely soluble (solution darkens after sitting for several days)
n-Propanol	Partially soluble
Methanol	Completely soluble
Ethanol	Completely soluble *took longer to dissolve than methanol but eventually all the material dissolved at r.t.
Toluene	Completely soluble
Methylene Chloride	Completely soluble
Acetonitrile	Completely soluble
Cyclohexanes	Insoluble
Ethyl Acetate	Completely soluble
Isobutyl alcohol	Insoluble
Water	Insoluble
50:50 (v/v) n-propanol/water	Insoluble
95:5 (v/v) ethanol/water	Partially soluble at r.t. *tried recrystallization of 10g crude with 95/5 ethanol/water and it was still quite soluble – multiple crops of solid would need to be isolated from the solution
50:50 (v/v) ethanol/water	Insoluble at r.t. *tried recrystallization of 10g crude with 50/50 ethanol/water and almost 1L of solvent was required to dissolve the material. Later found that the material had NOT completely dissolved and a waxy residue was present along with white needle-like crystals of cyanacure
80:20 (v/v) ethanol/water	Insoluble at r.t. *all dissolved when heated

Recrystallization Information:

The goal is to obtain a solvent or solvent combination for recrystallization that will allow almost complete recovery of the purified product in the 1st recrystallized crop. It is not optimal, especially for scale-up to have to continue isolating product from the solution, leading to a 2nd and 3rd crop of material.

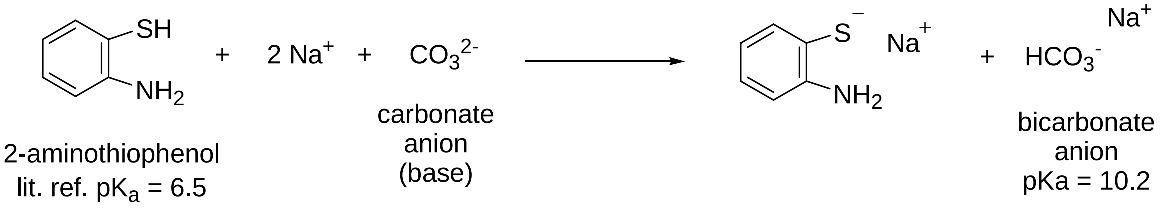
For recrystallization, you want a solvent in which the crude product is insoluble at room temperature and soluble when heated. The solvent of choice should have a boiling point below the melting point of your crude material. The reasonable solvent options for APO-Link are very limited. The crude APO-Link product is readily soluble in almost all common recrystallization solvents. For the solvents in which the crude is insoluble at room temperature, an extremely large volume of solvent would be required to achieve dissolution of the crude product, even with heating (i.e. hexanes or cyclohexane). Higher boiling alcohols, like iso-butylalcohol are also viscous and not really suitable for recrystallizations. Solvent considerations are complicated, especially for scale-up. You do not want to use anything that is highly flammable or toxic, of course, the KCP has a limited acceptable solvent list for plant use.

After all of these considerations, it was decided that different ratios of ethanol/water might be a reasonable option for recrystallization. The volume ratio of 95/5 ethanol/water was still quite soluble. The volume ratio of 50/50 ethanol/water was also used for recrystallization. However, approximately 900 mL of 50/50 ethanol/water was required for the recrystallization of about 10 g of crude product. After using 900 mL of hot solvent, it appeared that all of the material had dissolved. However, apparently there were insoluble oil droplets that cooled down to a yellow wax along with the needle-like cyancure crystals. Based on this, a good solvent combination is a volume ratio of 80/20 ethanol/water. A weight ratio of 80/20 ethanol/water was also used and acceptable.

Appendix VI

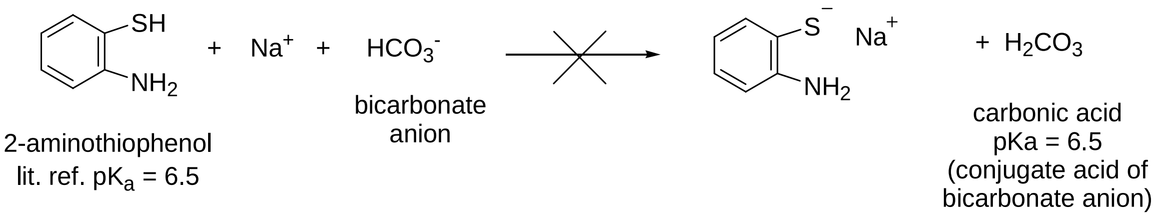
Acid-Base Chemistry of 2-Aminothiophenol

Deprotonation of ATP:



Scheme AVI-1. Deprotonation with carbonate base.

A 1:1 molar ratio between ATP and sodium carbonate results in the deprotonation of ATP with carbonate anion. The bicarbonate anion formed following the initial deprotonation with carbonate is not quite a strong enough base to deprotonate ATP.



Scheme AVI-2. Deprotonation of ATP is not likely with bicarbonate base.

As indicated above, bicarbonate is not quite strong enough to deprotonate ATP. ATP and carbonic acid (conjugate acid of bicarbonate) have approximately the same pKa value. In short, 1 mole of carbonate base is required to adequately deprotonate 1 mole of ATP before reaction with dibromo or dichloroethane.