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Development of Manufacturing Processes for a New Family of 2,6-Dihaloaryl 1,2,4-Triazole Insecticides

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Abstract:

Details are presented on the process development work for the new 2,6-dihaloaryl-1,2,4-triazole insecticide 1, and the development of a one-pot process toward a potential commercial manufacturing process.

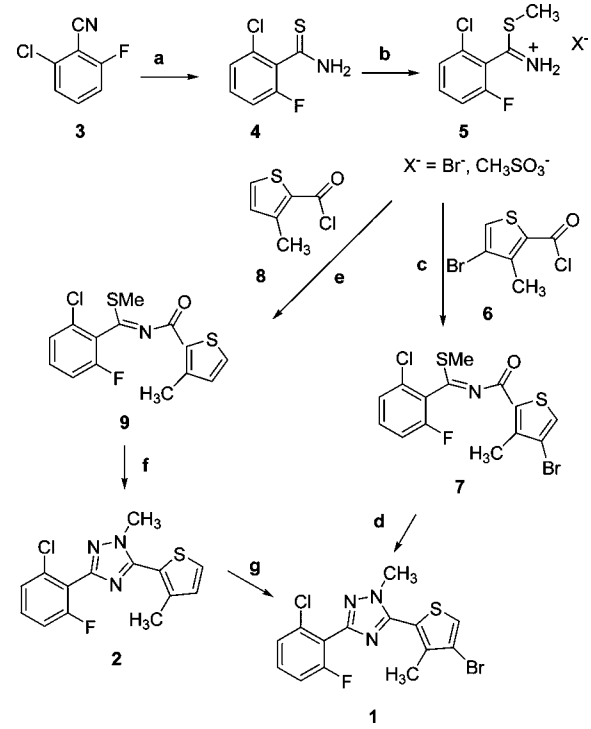
Introduction

Effective insecticides will continue to be a critical need for world agricultural markets, as it has been estimated that up to 15% of annual global food crops are lost to insects.[1] The search for safe and effective insecticides that exhibit low biopersistence and low mammalian and aquatic toxicity continues to be a significant agricultural challenge for the 21st century. The two major trends of an ever-growing world population together with the need for environmentally sustainable agricultural food products would sometimes appear to be at odds with one another. Dow AgroSciences has been investigating a new family of 2,6-dihaloaryl 1,2,4-triazole insecticides[2] featuring targeted insecticidal activity coupled with low mammalian toxicity.

We have previously reported laboratory results detailing our work on developing feasible synthetic routes for the thiophene ring of this class of compounds.[3] Synthetic methodologies were also developed for construction of the 2,3,4-triazole ring system, along with coupling strategies for these two heterocycles to afford the target 2,6-dihalo insecticides. This route, shown in Scheme 1, gave the desired product, 2,3,4-triazole **1**, in four to five steps, in good yield and high purity.

Although this route proved suitable as a laboratory process to provide initial quantities of material for biological screening, when kilogram quantities of **1** were required for field trials, the shortcomings of this route became unmanageable. For example, this laboratory process requires the solids isolation of three intermediates, along with the use of three different process solvents. Clearly, for the production of multikilogram quantities, as well as a potential manufacturing route, a more simplified pilot plant process having fewer unit operations was desirable that could lead ultimately to a low cost commercial scale process.

Scheme 1. **Routes to 2,6-dihaloaryl-1,2,4-triazoles 1 and 2**[a]



[a] Reaction conditions: (a) H_2S, Et_3N, 1,4-dioxane, <0 °C. (b) $(MeO)_2SO_2$, 1,4-dioxane, 80°C; or CH_3Br, 1,4-dioxane, 25−80 °C. (c) **6**, 3-picoline, 1,4-dioxane. (d) CH_3NHNH_2, 1,4-dioxane, 50% NaOH, 40−80 °C. (e) 3-Picoline, **8**, 23°C. (f) CH_3NHNH_2, 1,4-dioxane, 80 °C. (g) HOAc, NaOAc, Br_2, 80 °C; then Zn powder, 78 °C.

One of the recent trends in Dow Process R&D is to develop manufacturing routes which minimize the number of isolations and seeks to find common solvents to simplify recycle streams. In this work, we describe our efforts to develop a one-pot and common solvent process for the production of **1**.

Results and Discussion

The initial laboratory route for the preparation of **1** and **2** is shown in Scheme 1. 2-Chloro-6-fluorobenzonitrile **3** was treated with H_2S in Et_3N as the solvent, followed by methylation to give the thioamidate salt **5**. This is then coupled to a thiophene carboxylic acid chloride **6** or **8**, giving the thioamidate esters **7** and **9**. Finally, cyclization with methylhydrazine leads to the target compounds **1** and **2**. Alternatively, a bromination/reductive debromination of **2** also gives **1**.

For the development of a one-pot process to the triazoles **1** or **2**[4] a common solvent was preferred. All of the steps in the

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(1) McMurry, J. *Organic Chemistry*, 4th ed.; New York: Brooks/Cole Publishing Co; 1996, p 759.

(2) Cudworth, D. P.; Hegde, V. B.; Yap, M. C. H.; Guenthenspberger, K. A.; Hamilton, C. T.; Pechacek, J. T.; Johnson, P. L.; Bis, S. J.; Tisdell, F. E.; Dripps, J. E.; Bruce, T. J.; Dintenfass, L. P.; Gifford, J. M.; Karr, L. L.; Kempe, M. K.; McCormick, D'L. C.; Schoonover, J. R., Jr. *J. Agric. Food Chem.* **2007**, *55* (18), 7517.

(3) Hull, J. W.; Romer, D. R.; Podhorez, D. E.; Ash, M. L.; Brady, C. H. *Beilstein Journal of Organic Chemistry*; Clayden, J., Ed.; Beilstein Institut: Frankfurt, Germany, 2007; Vol. 3, p 23.

(4) Podhorez, D. E.; Hull, J. W., Jr.; Brady, C. H. U.S. Patent 6,096,898, 2000; CAN 133:135314.

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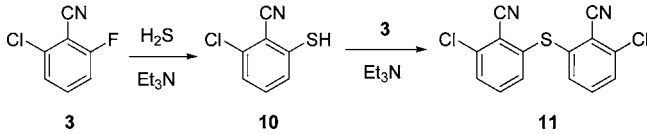
Scheme 2. **Thiol and thioether impurity formed in the thioamidation step**



3 **10** **11**

process were compatible with 1,4-dioxane, and this solvent was particularly convenient for isolation of the final products. By simply adding an excess of water to the reactor, a separation of the technical-grade product as an oil occurred. Therefore, we focused our efforts to develop a one-pot process for **1** using 1,4-dixoane as the common solvent for all reaction steps.

The key starting material, 2-chloro-6-fluorobenzonitrile **3**, was obtained from a 2,6-difluorobenzonitrile production plant as a 92 GC area % pure compound. Initial preparation of benzthioamide **4** from **3** was carried by the addition of H_2S gas to **3** in pyridine in the presence of Et_3N,[5,6] with the exception that the reaction temperature was lowered to <0 °C to minimize the formation of an undesired thiol byproduct **10** (Scheme 2). This thiol byproduct arises from the displacement of fluoride from **3** by H_2S, rather than attack on the cyano functionality, giving thiol **10**. The thiol can then undergo further coupling reactions with **3** in the presence of excess base to form higher thioethers **11**. Early laboratory experiments demonstrated that, by carrying out the thioamidation reaction at −10 to −20 °C, the coupling side reactions to form thioethers were minimized, and cleaner thioamidate **4** was isolated as a white microcrystalline solid by quenching the reaction mixture with water in which the thiol byproduct **10** was soluble.

Success in developing a one-pot process for a series of reaction steps hinges on the ability to remove certain reagents from the reaction mixture without isolating the key reaction intermediates. This can be accomplished in various ways by using aqueous wash steps, distillation operations, filtrations, and such. The first goal in developing a one-pot process for **1** or **2** was to eliminate the isolation of benzthioamide intermediate **4**, which would avoid the production of a large aqueous waste stream and a solids isolation step.

Fortunately, initial tests showed that using 1,4-dioxane solvent in place of pyridine in the thioamidation step led to high yields of **4** in solution, with minimal formation of the undesired byproduct **11**. However, in order to take advantage of this ability to use a common solvent across multiple reaction steps and eliminate the isolation of **4**, Et_3N base used during this thioamidation step must be removed from the reaction mixture to prevent its methylation to $MeEt_3N^+Br^-$ by MeBr in the subsequent reaction step. This quaternization reaction, while not directly interfering with the desired product chemistry, would consume an excess of methylating agent and produce a relatively large amount of quaternary ammonium salt in the waste stream. Initial attempts to remove excess Et_3N from the post thioamidation reaction mixture by distillation showed that this reaction is easily reversible. Thus, as excess H_2S was removed and moderate heat applied, **4** reverted back to the starting material **3** in the presence of Et_3N.

To circumvent this problem, the thioamidation reaction was investigated using catalytic levels of Et_3N, and this was found to be successful using 5−20 mol % of Et_3N based on starting material **3**. With this approach, Et_3N remained in the reaction mixture and was deactivated in the next step by methylation to the quaternary ammonium salt, now present at lower catalytic levels. This deactivation of Et_3N is critical, as it prevents reversion of **4** back to **3** upon application of heat and removal of residual H_2S. Also, excess residual H_2S was found not to be detrimental to the methylation reaction and could be removed from the reaction mixture after that step.

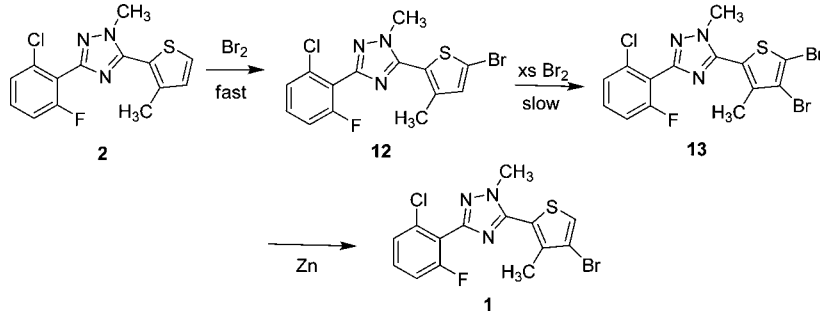
In practice, it was found that the most convenient approach to carrying out the thioamidation reaction was with a moderate H_2S pressure of 30 psig in a pressure vessel and heating at 60 °C in 1,4-dioxane solvent and 20 mol % Et_3N. This approach can also be readily applied to a commercial manufacturing scale. However, for laboratory development efforts, we used the following process under atmospheric conditions that could readily be adapted to operating under mild pressure ranges in a pilot-plant or commercial-scale process. The thioamidation reaction could be effectively carried out at atmospheric pressure in a standard jacketed glass reaction vessel by sparging H_2S gas into a 60 °C solution of **3** and catalytic Et_3N in 1,4-dioxane. A dry ice trap was applied to the reactor to condense liquid H_2S, and 1.5−1.7 mol equiv of H_2S gas sparged into the 60 °C solution as fast as the dry ice condenser allowed. In this manner the thioamidation reaction was carried out to high conversion within a 24 h period with >95 GC area % of **4** attainable.

Laboratory reactions had shown that methylation of **4** to give the thioamidate salt **5** was most conveniently accomplished with dimethylsulfate as the methylating agent. Using 1.3 mol equiv of dimethylsulfate, a quantitative conversion of **4** to **5** was achieved within 3 h at 75 °C. However dimethylsulfate is considered too hazardous for scale-up to a commercial process. Thus, the use of methyl bromide (MeBr) gas as the methylating agent was investigated. A higher molar excess of MeBr of 1.5−2.0 equiv and slightly higher temperature (80 °C) was required to attain high conversion of **4** to **5**. The 20 mol % of Et_3N remaining from the previous step reacted with MeBr to form the quaternary ammonium salt, and the excess H_2S prevented reversion of **4** back to **3**. During the course of MeBr addition, **5** (as the Br^- salt) precipitated from solution. After methylation, excess dissolved H_2S gas was removed from the reactor by a subsurface nitrogen sparge of the reaction mixture to sweep residual dissolved H_2S into a bleach scrubbing solution.

The coupling step to attach thiophene acid chloride **6** or **8** to the imine nitrogen of **5** (Scheme 1), to give either the thioimidate **7** or **9** required a pyridine base to promote the reaction. As both H_2S and MeBr will react with pyridine necessitating additional quantities of the base, a thorough sparging of the reaction mixture was required prior to the acylation coupling step to remove these two materials. Triethylamine (TEA), pyridine, and 3-picoline were investigated as bases in this step. TEA led to lower yields in the subsequent cyclization step with methylhydrazine. The other bases gave good results for both the coupling and subsequent cyclization steps, but 3-picoline was chosen on the basis of cost. At least

(5) Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.
(6) Abbas, K. A.; Edward, J. T. *Can. J. Chem.* **1985**, *63*, 3075.

Scheme 3. **Thiophene bromination chemistry**



two equivalents of 3-picoline are required, one to neutralize the acid equivalent in the protonated **5** salt and one to neutralize the HCl byproduct of the acylation. Laboratory results showed that 2.3−2.7 mol equiv of base were found to be most effective in terms of yield of the desired product and efficiency of the reaction.

Small-scale laboratory studies had shown that the methylhydrazine cyclization step to produce the 2,6-dihalo-aryl-1,2,4-triazoles **1** or **2** could be carried out without isolation of the thioimidates intermediates **7** or **9**. The use of a strong base was required, and 50% aqueous NaOH was the base of choice for this step. Two molar equivalents of methylhydrazine was added to the reaction mixture, followed by 50% aqueous NaOH, and the reaction mixture was heated at 80 °C to effect conversion to the triazole ring system. In this step, sodium methanethiolate is produced as a stoichiometric byproduct. Thus, a slightly basic pH was maintained to control the stench of methanethiol.

Isolation of **1** obtained via bromothiophene **6** was accomplished by dilution of the reaction mixture with water and separation of crude **1** as an oil. The oil was readily separated from the aqueous phase as the bottom phase and was then added to aqueous ethanol with cooling to effect precipitation of **1** as a tan solid with a purity of 95 wt %. The isolated yield of technical-grade **1** was 69% based on **3** and 65% based on **6** as starting materials. The final product **1** could be further purified by recrystallization from warm 2-propanol to give a product purity of 99 wt %, which also ameliorated the disagreeable thiol odor.

The final step to **1** via thiophene **8** was carried out using a bromination/debromination approach (Scheme 3). A benefit to this process is bromine effectively oxidizes all residual thiols remaining in **2**, and odor-free **1** is obtained from the reaction. Although the production of **2** was also compatible with the one-pot process using 1,4-dioxane as the common solvent, the bromination/debromination step was not, and therefore **2** must be isolated prior to bromination.

The bromination of **2** requires an excess of Br_2 to achieve full conversion to the dibromide. The first bromination is rapid and exothermic, presumably forming the initial α-bromo intermediate **12**. However, the second bromination, placing a bromine atom on the deactivated 4-position of the thiophene ring, required an additional 3 equiv of bromine and 6 h at 80 °C to produce **13**.

Initially charging 4 equiv of Br_2 in acetic acid allowed for the rapid and clean conversion of **2** to **13** after 1 h at 80 °C. To carry out a "one-pot" approach, water was added to the reactor after the bromination step was complete, and an excess of zinc powder was used to quench the two extra equivalents of Br_2. This is an exothermic reaction (−95 kcal/mol)[7] and was controlled by the addition of zinc powder to the reactor in small portions.

A total of 4 mol equiv of zinc were used to quench the excess bromine and effect the debromination reaction to give **1**. The debromination reaction of **13** to give **1** was highly selective for only removal of the ortho bromine, even with an excess of zinc powder and extended heating at 80 °C; for example, the reaction mixture can be stirred overnight at 80 °C without side reactions.

As a note of caution, the addition of excess zinc powder to a solution of aqueous acetic acid leads to the evolution of H_2 gas along with the production of zinc acetate salt. *Thus, precautions were taken against flammability and explosion hazards*. Knowledge of the explosion limits of hydrogen/nitrogen mixtures is essential at this step to allow for sufficient dilution of the reactor head space with a nitrogen purge stream in order to remain outside the flammability window.

Each of the two routes to **1** had certain advantages over the other. The availability of bromothiophene **6** allowed for the assembly of **1** with the bromine prepositioned on the thiophene ring. However, this route also requires a recrystallization step to produce low-odor material, a critical aspect of product integrity for a commercial process. Use of the thiophene building-block **8** gives the 2,6-dihalo product **2**, which requires additional bromination/debromination steps to prepare **1**. However, this route also gives low-odor material without a cleanup step required. Also, certain processing challenges exist with the bromination/debromination of **2** to **1**, which requires the careful addition of zinc powder in a highly exothermic reaction, and the generation of hydrogen gas as a coproduct. Thus, due to the general ease of operation and the availability of a process to the bromothiophene building-block **6** as previously reported,[3] the bromothiophene route using **6** was favored to advance. The route to **1** via **6** and **7** was readily applied on a multikilogram scale using 22-L glass reactors in a laboratory pilot-plant operation. The challenge of odor present in technical-grade **1** obtained from this route was addressed with a single recrystallization from 2-propanol, which also served to enhance the chemical purity. Thus, a high-grade product was readily obtained with this route as defined by low odor and high chemical purity.

(7) *The NBS Tables of Chemical Thermodynamic Properties*; J. Phys. Chem. Ref. Data, Vol. 11, Suppl. 2, NSRDS, U.S. Government Printing Office: Washington, DC, 1982.

Summary and Conclusion

A one-pot process has been developed as a preliminary process to produce the new 1,2,4-triazole experimental insecticide **1**. This one-pot process has been used to prepare kilogram quantities of the triazole compound. 1,4-Dioxane was found to be an effective solvent for all reaction steps except the bromination/debromination step for the conversion of **2** to **1**, thus requiring a single isolation. The process for **1** utilizing the brominated thiophene intermediate **6** produced **1** containing some odoriferous residual sulfur compounds, while the bromination/debromination route from **2** produced odor-free technical-grade product. Thus, the bromothiophene route required a final recrystallization step to obtain low-odor product. For the bromothiophene one-pot process, a 69% isolated technical-grade yield of **1** based on **3** and 65% based on **6** was obtained. The purity of the technical-grade material was 96%. Final recrystallization to obtain low-odor product gave an 86% recovery as a first crop from 2-propanol, resulting in an overall isolated yield of 56−59% of **1** with a final chemical purity of 99+%.

Experimental Section

Raw Materials. Kilogram quantities of 3-methyl-2-thiophenecarbonyl chloride (**6**) and 2-chloro-6-fluorobenzonitrile (**3**) were purchased from Lancaster Synthesis.[8] Preparation of 3-methyl-thiophenecarbonyl chloride (**6**) and 4-bromo-3-methyl-2-thiophenecarbonyl chloride (**8**) has been reported separately.[3] Samples of **6** and **8** were also purchased in 5 kg research quantities from Shasun Chemical and Drugs, Ltd. of India.[9]

Reverse-phase HPLC Conditions: Zorbax Rx C8 column, 4.6 × 250 mm; UV detector at 220 nm; 60/40 CH_3CN/H_2O with 0.07 wt. % H_3PO_4 at 1.0 mL/min flow rate; biphenyl as internal standard for reaction samples, benzophenone as internal standard for assay of **1**. Retention times (min): **5**, 3.4; **4**, 3.9; **3**, 5.6; **1**; 9.2.

GC Conditions: DB-5 column, 15 m × 0.53 mm, 1.5 μm film; FID detector, N_2 carrier gas; oven heating 60 °C for 3 min, 15 °C/min to 250 °C for 5 min; biphenyl as internal standard for reaction samples, benzophenone as internal standard for assay of **1**. Retention times (min): **3**, 6.9; **6**, 9.4; **4**, 11.7; **7**, 17.5; **1**, 17.8.

Elemental analyses were performed by Galbraith Laboratories.

Technical-grade **3** was obtained from a Dow AgroSciences production facility as a byproduct of another process that was distilled to give a 92% pure material by GC area % and further purified by recrystallization. Details of the purification of 2-chloro-6-fluorobenzonitrile **3** by batch recrystallization and the isolation of reaction intermediates can be found in the Supporting Information.

Handling H_2S Gas. *Caution! Hydrogen sulfide gas is flammable and toxic and may be fatal with sufficient exposure. It is an insidious poison in that the sense of smell can be fatigued and lead to an inability to detect high concentrations. It should be handled only by qualified personnel in a well-ventilated fume hood using a bleach/NaOH scrubber system to quench excess amounts venting from the reactor. In order to readily and quickly detect the presence of any fugitive H_2S emission from the reactor and scrubber systems, H_2S detector tape was obtained from MDA Scientific (H_2S Chemcassette LP part number 711304) and used inside the hood and around the reactor and scrubber glass joints and at the scrubber vent. This paper tape is capable of detecting very low ppm levels of H_2S that allowed for the quick repair of any leaking joints. In this manner fugitive H_2S gas emissions into the hood and atmosphere were minimized.*

One-Pot Process to 1 using Brominated Thiophene 6. *Step 1. Thioamidation of 3.* A 22 L jacketed glass reactor was fitted with a dry ice condenser, and the condenser was vented to a bleach reservoir containing 20 L of 12% bleach solution. Under a N_2 purge the vessel was charged with 1,4-dioxane (6000 mL), Et_3N (130 g, 180 mL, 1.3 mol), and 2-chloro-6-fluorobenzonitrile (**3**) (1000 g, 6.43 mol). While the stirring mixture became homogeneous, the condenser was cooled with dry ice/2-propanol. The jacketed vessel was heated to 60 °C, and hydrogen sulfide gas (375 g, 11.0 mol) was introduced below the surface of the stirring solution. Approximately 80% of the H_2S was added during an 8 h shift, with the remainder added the following morning after holding the reactor temperature overnight at 60 °C. The H_2S addition rate was manually regulated to control the bleach scrubber solution temperature to >25 °C and the reflux rate. The reaction mixture was stirred overnight at 60 °C and then sampled by HPLC to ensure complete conversion to 2-chloro-6-fluorothiobenzamide **4** and then cooled to 25 °C.

Step 2. Methylation of 4. The same vessel described above, including the dry ice/2-propanol condenser, was used for the methylation reaction. However, the bleach scrubber was vented to a trap containing 1.5 L of perchloroethylene. A heat lamp was used on the MeBr (bp 4 °C) lecture bottle to increase the gas-flow rate. Aluminum foil was used to protect the reactor from the light of the heating lamp. To the stirring, dark-brown reaction solution of **4** at 25 °C was added MeBr gas (800−900 g, 8.4−9.5 mol) over 5 h. After a third of the MeBr had been added, the vessel was heated to 80 °C for completion of the MeBr gas addition. During the gas addition the reaction mixture changed from a dark-brown solution to an orange solution and then to a yellow slurry. The mixture was stirred at 80 °C for 6 h and then was analyzed by GC for >98% conversion of **4** to methyl 2-chloro-6-fluorothiobenzimidate bromide salt (**5**). A subsurface N_2 purge was introduced to the mixture for 11 h, while the dry ice condenser came to ambient temperature and the reaction slurry was cooled to 40 °C. The N_2 purge was discontinued after no additional H_2S was detected at the reactor vent by detector paper.

Step 3. Coupling of 5 with 4-bromo-3-methyl-2-thiophenecarbonyl Chloride (6). The dry ice condenser on the 22 L reactor from above was replaced with a water condenser. The reactor jacket temperature was set to 20 °C, and 3-picoline (1359 g, 16.4 mol) was added over 20 min via peristaltic pump. During the addition, the internal reaction temperature remained <50 °C. The initial yellow slurry became an orange solution after stirring for 15 min after 3-picoline addition was completed. The jacket temperature was set to 10 °C, and **6** (2720 g, 6.81 mol) as a 60 wt % solution by volume in 1,4-dioxane was added to

(8) Lancaster Synthesis. Now a part of Alfa Aesar, a Johnson Matthey company; www.alfa.com.
(9) Shasun Chemical and Drugs, Ltd. of India. www.shasun.com.

the reactor over a 1 h period via peristaltic pump. The addition rate of **6** was adjusted such that the internal reactor temperature remained below 50 °C. After the addition was completed, the mixture was stirred at 10 °C jacket temperature for an additional 2 h. Analysis of a reaction sample by GC indicated that quantitative conversion of **5** to **7** had occurred.

Step 4. Cyclization of 7 to 1. The 22 L jacketed vessel from above was heated to 40 °C, and 98% methylhydrazine (440 g, 9.98 mol) was added to the reactor via peristaltic pump over 1 h. Immediately following the addition, 50% NaOH (1029 g, 12.9 mol) was introduced to the vessel at 43 °C over 1 h, or at a sufficient rate so as to maintain the reaction temperature below 50 °C. After completion of the addition of NaOH, the reaction mixture was stirred at 80 °C for 15 h. After this time a GC analysis indicated >98 area % conversion of **7** to **1**. The reaction mixture was cooled to 50 °C and sparged with N_2 for 1 h. Water (10.6 L) was added via pump and the reactor temperature re-established at 50 °C. The stirring was halted, and the phases slowly separated over 2−3 h. The dark-brown bottom organic phase along with a small emulsion layer was removed from the reactor at 50 °C and placed in bottles.

Step 5. Crystallization/Isolation of 1. A 12 L jacketed vessel was charged with 95% EtOH (2790 mL) and water (1200 mL). The crude oil from step 4 above was added over 15 min to the stirring EtOH/H_2O solution. The vessel jacket was set to 20 °C and stirred for 2 h. The solid product, **1**, precipitated from the solution and was collected through the bottom drain into a coarse filter crock via vacuum filtration. The wet cake was washed with 50/50 EtOH/H_2O (1 L) and allowed to dry overnight in the crock under a flow of N_2. The wet cake was air-dried in a glass tray to constant weight, over 7 d, to give ∼1800 g of technical-grade **1** as a tan solid, with a purity of 95% by HPLC assay method (4.42 moles based on assay). This technical-grade solid product exhibited a disagreeable odor.

Recrystallization of 1. A 2000 g sample of technical-grade **1** was dissolved into warm 2-propanol (7.2 L) at 75 °C. Cooling the solution to 15 °C gave solid **1** which was collected on a filter, rinsed with about 500 mL of fresh 2-propanol, and air-dried in a glass tray to a constant weight over 24 h to give 1731 g of **1** (86.6% recovery), as a tan solid with only a faint odor present, and an HPLC assay of >99% purity; mp 120−121 °C.

Preparation of an Analytical Standard of 1. A 554 g sample of recrystallized **1** from above was dissolved in CH_2Cl_2 and passed through a short column of silica gel. The eluant was stripped to dryness, recrystallized from warm 2-propanol (1270 g) as above, and air-dried to give 519 g (93.7% recovery) of **1** as a pale-yellow solid; mp 121−123 °C, 111 ppm water by Karl Fischer titration, and an HPLC and GC area % purity of >99%; ^{1}H NMR ($CDCl_3$): δ 7.4 (s, 1 H), 7.3 (m, 2 H), 7.1 (t, 1 H), 4.0 (s, 3 H), 2.3 (s, 3 H); ^{13}C NMR δ 163.2, 159.8, 155.0, 149.4, 139.8, 135.6, 131.2, 125.6, 122.2, 120.0, 114.6, 114.3, 36.9, 15.4. Anal. Calcd for $C_{14}H_{10}BrClFN_3S$ C, 43.49; H, 2.61; N, 10.87. Found: C, 43.44; H, 2.52; N, 10.77.

Supporting Information Available

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

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