Organic Process Research & Development **2002**, *6*, 357−366

Articles

Process Research on the Synthesis of Silthiofam: A Novel Fungicide for Wheat

Gary Phillips, Thomas L. Fevig,* Patrick H. Lau, George H. Klemm, Michael K. Mao, Chun Ma, James A. Gloeckner, and Art S. Clark

Global Chemical Process Research and Development, Pharmacia Corporation, 800 North Lindbergh Boulevard, Mail Zone U3C, St. Louis, Missouri 63167, U.S.A.

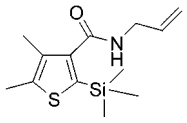
Abstract:

The development of an efficient, low-cost synthesis of the novel wheat fungicide silthiofam (1) is described. Improvements to the original Discovery route allowed 300 kg of material to be prepared in two, overlapping pilot-plant campaigns. Thereafter, efforts were focused on further optimizing the pilot-plant route, and on devising alternate, lower cost routes to silthiofam. One potential new route involved a cycloaddition reaction between 3-mercapto-2-butanone and *N*-(2-propenyl)-3-trimethylsilylpropynamide. The cyclic product could be directly dehydrated to silthiofam, however the overall yield was modest, raw material costs were high, and there were purification problems. The route ultimately selected for development proceeds in 6 chemical steps and about 60% yield from the inexpensive precursors 3-chloro-2-butanone and methyl 3-methoxyacrylate. Key features of the route are a novel thiophene-3-carboxylate synthesis involving cycloaddition of 3-mercapto-2-butanone with the acrylate followed by acid catalyzed aromatization, the room temperature formation and silylation of a thiophene-3-carboxylate dianion, and conversion of the resulting carboxylic acid into silthiofam with negligible loss of the silyl group. The process involves isolation of just two intermediates, only one of which is purified, and uses only three organic solvents, all of which are recycled. It can be run safely on large scale to give high-purity silthiofam.

Introduction

Take-All is the common name for a serious disease of cereal crops caused by the soil borne fungus *Gaeumannomyces graminis*. The fungus attacks the roots of the host plant, preventing it from obtaining adequate water and nutrients, resulting in poor plant vigor, and in severe cases, barren or very low-yielding plants. As the name implies, the yield loss associated with the disease can be devastating, up to 50%, although the infection is not lethal to the host plant. In addition to the yield loss, the threat of infection can cause farmers to rotate fields to less profitable crops for up to 3 years. There are no varieties of wheat or barley resistant to the disease. In light of these facts, Take-All is considered the most damaging root disease of cereal crops worldwide,[1] and therefore fungicidal agents active against Take-All are highly desirable.

In 1989, a compound active against *G. graminis* was found through a random screening process at Monsanto.[2] Extensive SAR studies ultimately led to the selection (in 1995) of 4,5-dimethyl-*N*-(2-propenyl)-2-trimethylsilyl-3-thiophenecarboxamide (**1**, silthiofam) as a commercial candidate.[3] The compound is applied as a seed treatment and is properly termed a fungistat, since it protects the cereal plant from the effects of the fungus outlined above, but does not kill the fungus. In 1999, Monsanto began marketing a formulation containing silthiofam under the trade name Latitude. We describe herein the development of a process for the synthesis of silthiofam. The work highlights the rigorous cost-saving measures necessary to develop an agricultural product, the commercial success of which is totally dependent on achieving a very low cost of goods. These measures include developing a route from the cheapest possible raw materials, minimizing the number of steps, intermediate isolations, and purifications, reducing the usage of expensive reagents, and recycling solvents and avoiding solvent switches.



1, Silthiofam

Results and Discussion

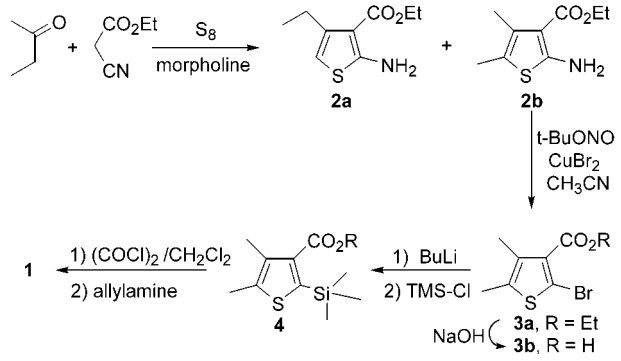
Original Discovery Route to 1. The route to **1** developed by the Discovery chemists is shown in Scheme 1.[3] It involves construction of the thiophene ring very early in the sequence by the Gewald aminothiophene synthesis.[4] A Sandmeyer

* To whom correspondence should be addressed. E-mail: thomas.l.fevig@pharmacia.com. Telephone: 314-694-4864. Fax: 314-694-1621.

(1) Take-All Disease of Cereals. *Home Grown Cereals Authority Research Review*, No.20; 1991. See also *Biology and Control of Take-All*; M.J.C. Asher, M. J. C., Shipton. P. J., Eds.; Academic Press: New York, 1981.
(2) The original hit was a sample from Professor Victor Snieckus' group at University Waterloo.
(3) Phillion, D.; Wong, S. C.; Shortt, B. U.S. Patent 5,486,621A, 1996.
(4) For a review of the Gewald synthesis, see: Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, *36*, 333. For a recent review of thiophene synthesis, see: Nakayama, Juzo. Thiophenes and their Benzo Derivatives: Synthesis. *Compr. Heterocycl. Chem. II* **1996**, *2*, 607−677.

10.1021/op020206f CCC: $22.00
Published on Web 05/10/2002

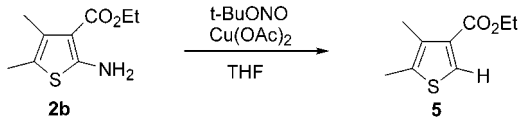
Scheme 1



reaction provided bromoester **3a**, which was hydrolyzed, and treated sequentially with *n*-BuLi and trimethylsilyl chloride to afford silyl acid **4**. Acid **4** (R = H) was converted into **1** by standard methods.

A preliminary run-through of the sequence revealed several significant issues that needed resolution. The overall yield was very low, about 2%. The Gewald reaction produces mainly **2b**, but also a significant amount of the isomeric byproduct **2a**, which is carried all the way through to the final product, and the mixture was not initially separable. The Sandmeyer reaction[5] involves use of a hazardous reagent (*t*-BuONO), and gives a modest yield of product. The bromo acid **3b** filters very poorly. The silylation reaction, though efficient, was run at very low temperature (−70 °C). Finally, formation of the acid chloride is accompanied by a substantial amount of desilylation (> 20%), necessitating chromatographic purification of the final product.

Process Improvements Prior to Pilot-Plant Campaign. Because of the urgent need for large amounts of **1** for toxicology range-finding studies (20 kg) and two-year field trials (200 kg), it was decided to modify this route, addressing the problems outlined above, and run it in the pilot plant to obtain the required material, even though it was considered unlikely that the modifications would result in a commercially viable process. In preparation for the pilot-plant runs, several improvements were made. Although the ratio of isomers formed in the Gewald reaction could not be improved, a simple wash procedure was developed that allowed removal of the ethyl isomer **2a** with a tolerable recovery of the desired isomer **2b**. The Discovery chemists[3] found that the silyl group could be put in through a deprotonation process[6] rather than the halogen−metal exchange originally used. This reaction with lithium diisopropylamide (LDA) as the base could be run at 0 °C as opposed to −70 °C, and eliminated the difficult-to-handle bromo acid as an intermediate. However, this change required development of a reductive deamination procedure to replace the Sandmeyer reaction. It was ultimately found that by changing the solvent[7] and copper salt used in the Sandmeyer conditions, a moderate yield of the protio compound **5** could be obtained.



The major improvement on the back end of the process was using thionyl chloride in toluene to generate the acid chloride. Under these conditions, the yield was nearly doubled, and desilylation was reduced to ca. 10%, allowing the final product **1** to be isolated by crystallization from heptane instead of by chromatography.

Initial Pilot-Plant Campaign. The material for toxicology trials was prepared in two pilot-plant runs. The first was carried out in 100-gal equipment with the goal of preparing at least 20 kg of **1**. While the early steps in the sequence were running in the pilot plant, the later steps were being further defined in the laboratory. Scale-up information obtained in the 100-gal run was then immediately applied to the second, overlapping campaign in 750-gal reactors. In this way, 20 kg of material was prepared for the toxicology range-finding studies, and 300 kg of **1** was obtained for the two-year trials. Both campaigns were completed on schedule and provided final product in >98% purity. All of the process improvements were demonstrated, and the 2% yield of the original synthesis was increased to 10% yield upon scale-up.

For the following discussion, the pilot-plant route is conveniently divided into three stages: thiophene ring synthesis, hydrolysis/silylation, and amide formation. Upon reviewing the pilot-plant results, it became apparent that significant obstacles had to be overcome in each stage before this route could approach commercial viability. Moreover, the improvements required at each stage were of comparable value according to cost calculations and other factors, and were therefore addressed simultaneously. For example, increasing the low yield (∼20%) in stage 1, due to the formation of isomers and an inefficient deamination, could potentially lower the overall cost about as much as improving the modest yield (68%) in stage 3, caused mainly by competing desilylation during acid chloride formation. Although stage 2 proceeded in much higher yield than the other stages, similar savings could potentially be achieved by reducing usage of BuLi and running the silylation step in such a way that the expensive THF could be recycled.

In addition to improving the pilot-plant route as above, alternate synthetic routes were investigated in parallel, the goal being to develop a lower cost manufacturing route circumventing all of the particular problems of the pilot-plant route.

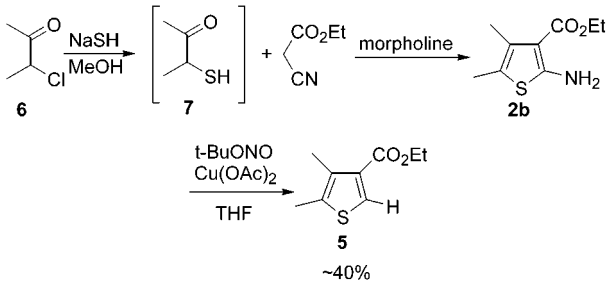
Optimization of the Pilot-Plant Route. The first stage of the pilot-plant route, the synthesis of thiophene ester **5**, suffers from low overall yield (ca. 20%), high waste load,

(5) Doyle, M. P.; Siegfried, B.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2426. For reviews of the Sandmeyer reaction, see: *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Eds.; John Wiley: New York, 1978; Hodgson, H. H. *Chem Rev.* **1947**, *40*, 251.

(6) There is literature precedent for this process. See: Beese, G.; Keay, B. A. *Synlett* **1991**, 33 and references therein.

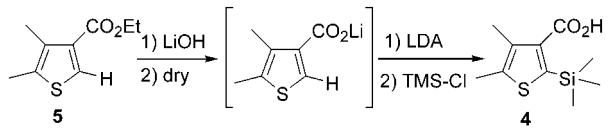
(7) Cadogan, J. J. G.; Molina, G. A. *J. Chem. Soc., Perkin Trans. I* **1973**, 541. For a review on deamination of aromatic amines, see Kornblum, N. *Org. React.* **1944**, *2*, 262.

use of a hazardous reagent, and the requirement of an isomer separation. The isomer problem was solved by preparing 3-mercapto-2-butanone **7**, a Gewald reaction intermediate, from the readily available 3-chloro-2-butanone (**6**) and NaSH. The mercaptan was not isolated, but used in situ in the Gewald reaction, thereby increasing the yield of aminothiophene **2b** to 70% (unoptimized) from 40%, and simplifying the workup. Although the new raw materials are somewhat more costly than butanone and sulfur, these improvements more than made up for the added raw material cost. Unfortunately, despite extensive effort the deamination could not be improved, leaving the overall yield of **5** at about 40%.



6 7 2b 5 ~40%

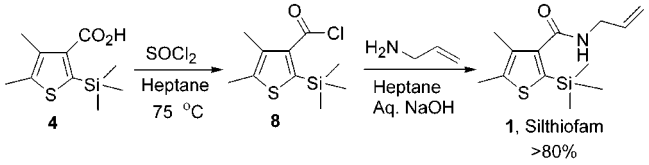
In the pilot-plant runs, the ester **5** was hydrolyzed, and the free acid was isolated. Removal of the ring hydrogen prior to silylation then required the use of 2 equiv of LDA, one of which simply generated the carboxylate salt. Since LDA is an expensive raw material, a new procedure was developed in order to reduce the usage of this reagent. The ester was hydrolyzed with LiOH instead of NaOH,[8] and rather than isolating the free acid with an acid/base workup, the resulting lithium carboxylate was azeotropically dried and submitted to the silylation conditions, but using only 1 equiv of LDA. This tactic proved quite successful, and a ca. 90% yield of **4** could be obtained. A further cost reduction was achieved by generating LDA in situ from diisopropylamine (DIPA) and *n*-BuLi rather than purchasing LDA solution. It was sufficient to use only 0.5 equiv of DIPA in this reaction. In addition to reducing usage of BuLi and DIPA and eliminating a solid isolation, the new procedure seemed amenable to incorporation of a THF recycle step (discussed below).



5 4 ~90%

Finally, the last stage of the synthesis was considerably improved by performing the chlorination in heptane. This reduced the total number of process solvents and allowed a solvent switch between steps 5 and 6 to be avoided. Desilylation was further reduced (to less than 1%), consistent with the previous observation that nonpolar solvents (toluene) were superior to more polar solvents (CH_2Cl_2) in this regard. This could be due to low solubility of the byproduct HCl in the nonpolar solvents, or such solvents could inhibit formation of the polar, protonated intermediate that leads to desilylation. The allyl amide is then formed from acid chloride **8** in a two-phase mixture of heptane and aqueous NaOH, and the product is crystallized from the heptane phase after the reaction (Scheme 2). The yield of silthiofam from

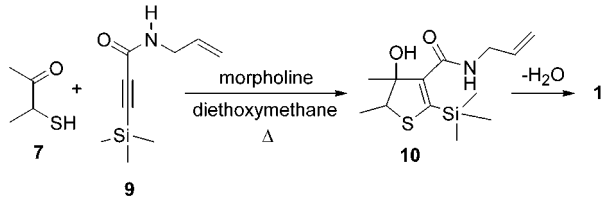
Scheme 2



4 8 1, Silthiofam >80%

acid **4** is increased to >80% by this modification, compared to the 68% yield obtained in the pilot plant.

Alternate Route Investigations. Incorporation of all of the above changes brought the overall yield of silthiofam to about 30% from chlorobutanone **6**, and markedly reduced the cost. However, while these improvements were being developed, investigations were continued in parallel in hope of finding a still lower cost, alternative route to **1**. Among many routes examined, the most promising is shown below. In this convergent approach, the thiophene ring is generated late in the sequence, in contrast to the pilot-plant route. In the key step, mercaptobutanone **7** reacted with acetylenic amide **9** in the presence of an amine base to afford the tertiary alcohol **10** in up to 83% yield with respect to **9**.[9] Compound **10** can be dehydrated to silthiofam.



7 9 10 1

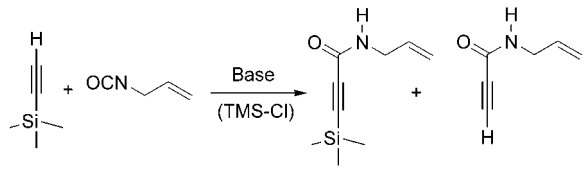
The obvious appeals of this route were the short length and high yield. However, these potential advantages were dependent on economical access to both **7** and **9**. Not surprisingly, neither compound was commercially available in bulk quantity. Although a synthesis of **7** had already been developed, it employed MeOH as solvent, whereas an aprotic solvent is optimal for the cycloaddition. In principle, a solvent exchange could be done, but this was never investigated for reasons that are given below.

Obtaining compound **9** economically proved to be a bigger problem. The material used to explore the cycloaddition chemistry was prepared by standard methods from a small commercial sample of the corresponding silyl propiolate ester. However, neither this compound, nor any other propiolate esters or acids were available in large quantity. Therefore, a new synthesis of **9** was needed. The first approach attempted (shown below) involved reaction of allyl isocyanate with the readily available trimethylsilyl-

(8) Using a mixed Na/Li salt gave lower yields; therefore, the more expensive LiOH was used for the hydrolysis.

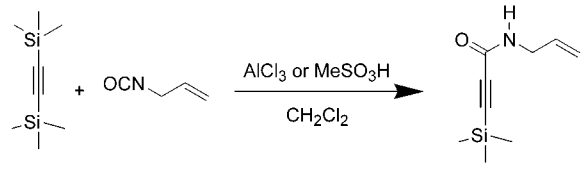
(9) Phillips, W. G.; Mao, M. K.; Ma, C.; Fevig, T. L. U.S. Patent 6,140,511, October 31, 2000. An approach to thiophene carboxylates involving reaction of propiolate esters and α-mercaptoketones in the presence of KOtBu in DMSO has been reported, but the yields were generally low (7−58%). See, Bohlmann, F.; Bresinsky, E. *Chem. Ber.* **1964**, *97*, (8), 2109.

acetylene in the presence of a strong base (LDA, Grignard, BuLi, etc.). While this reaction was successful, the yields were always low owing to desilylation of the product. The desilylation could be minimized by adding an equivalent of TMS-Cl to the reaction, but the yield was still only about 50%.



9

An acid-catalyzed approach was also investigated, with bis(trimethylsilyl)acetylene and allyl isocyanate as the substrates.[10] A potential advantage of this reaction is that no expensive, strong base would be required. Two effective acid catalysts were found, $AlCl_3$ and $MeSO_3H$, with the latter giving higher yields. Although a chemical yield of up to 77% can be obtained, the reaction always gives a significant amount of tar due to the fact that each substrate is rapidly decomposed by the catalyst. This also dictates that neither substrate can be present in excess, either by stoichiometry or by order of addition.

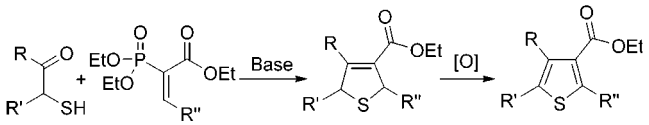


9

Although **9** can be purified by distillation, the material is a very high-boiling oil that tends to decompose during distillation above 100 °C (<1 mmHg), limiting isolated yields to 50−55%. To avoid this yield loss, the crude compound was carried through the sequence. The impurities did not seem to affect the chemistry significantly but caused severe problems in product isolation. Thus, the final product required chromatographic purification to give an isolated yield of about 30% from bis(trimethylsilyl)acetylene. While further experimentation may have improved on this result, it eventually became apparent that the raw material costs of this route were simply too high. Therefore, effort was refocused on the modified pilot-plant route, particularly the troublesome front end of the synthesis.

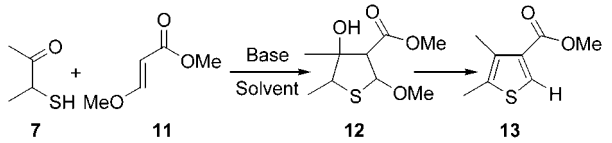
Development of a New Front End for the Pilot-Plant Route. The successful cycloaddition reaction between **7** and **9** to give **10** encouraged exploration of this type of route to ester **5**. In contrast to the acetylene derivatives mentioned above, many acrylates are available in bulk and are inexpensive, and might reasonably be expected to undergo the same type of reaction with mercaptoketone **7**. A search of the literature turned up a few examples of the synthesis of thiophene-3-carboxylates by reaction of α-mercaptoketones with acrylate esters.[11] In these cases, the acrylates were substituted at the 2-position with phosphorus groups, which facilitated ring closure by a Wittig-type process (Scheme 3).

Scheme 3



Subsequent oxidation gave the thiophenes.

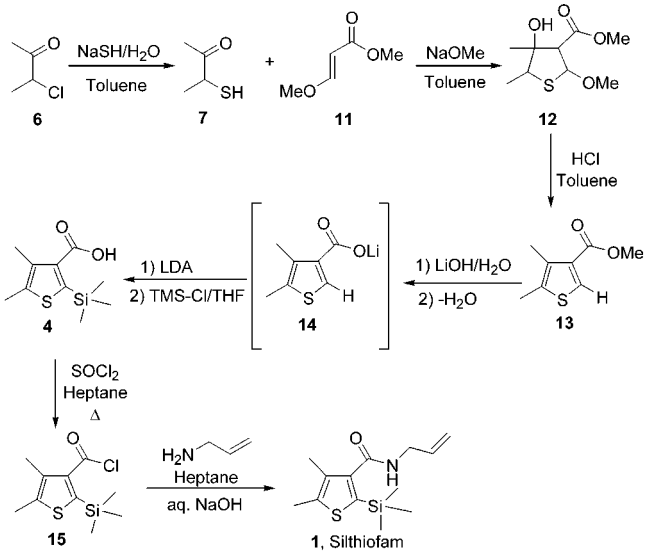
Two drawbacks of this particular route to thiophene-3-carboxylates are the added cost and waste issues associated with the phosphorus substituent, and the requirement of the oxidation step. The successful reaction of mercaptobutanone **7** with acetylenic amide **9** to give **10** in high yield (see above) led to the speculation that the phosphorus substituent may not always be required, depending on the substrates and reaction conditions employed. A separate oxidation step was also considered avoidable if an "oxidized" acrylate, or acetylene equivalent, could be used. Thus, the reaction sequence shown below was conceived.



7 **11** **12** **13**

Methyl 3-methoxyacrylate **11** is a relatively inexpensive material available on large scale. Treatment of this substrate with a small commercial sample of mercaptan **7** under various conditions afforded the tetrahydrothiophene derivative **12**, which could be isolated and purified. Subsequent treatment of **12** with acid effected elimination of methanol and water to provide the aromatic product **13**. A survey of bases and solvents in the cycloaddition step, and acids in the aromatization step led to the selection of NaOMe/toluene, and concentrated HCl/toluene, respectively, as described

Scheme 4

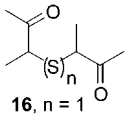


6 **7** **11** **12** **13** **14** **4** **15** **1**, Silthiofam

(10) Although we could find no direct precedent for this reaction, silyl acetylenes are well-known to react with acid chlorides to give ynones, and stannyl acetylenes are known to react with isocyanates to give acetylenic amides. See, respectively: Stang, P. J.; Dixit, V. *Synthesis* **1985**, 962; Kobs, U.; Neumann, W. P. *Chem. Ber*. **1990**, *123* (11), 2191.

elsewhere.[12] These choices necessitated the development of an alternate synthesis of **7**, formerly prepared from 3-chloro-2-butanone **6** and NaSH in MeOH. By performing the same reaction instead in a two-phase system of toluene and water, the toluene solution of **7** could be carried directly into the subsequent steps, thereby avoiding a solvent switch. This new synthesis of methyl ester **13** proceeded in ca. 75% isolated yield from the inexpensive chlorobutanone **6**, compared with the 40% yield of the existing route to ethyl ester **5**. It also demonstrated higher throughput, generated less waste, avoided hazardous reagents and extreme reaction conditions, and was operationally simpler. With this finding, the new route shown in Scheme 4 was selected for development in late 1997 and was demonstrated in a 100-gal pilot-plant run in mid 1998. The remainder of this paper will describe optimization of the process.

Optimization of the New Route. Step 1 of the process involves the reaction of chlorobutanone **6** with NaSH in toluene/water to give the mercaptan **7**. The observed byproducts are almost entirely derived from impurities in the starting materials. For example the major byproducts, sulfide **16** and disulfide **17**, are believed to result mainly from known contaminants, Na_2S and Na_2S_2, in the NaSH, since these products only increase slightly at higher temperatures and with prolonged reaction times.



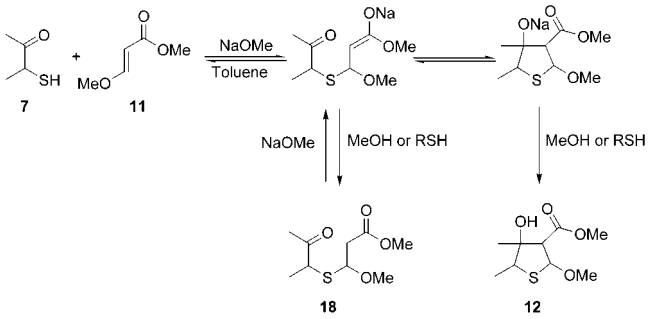
16, n = 1
17, n = 2

Since byproduct formation can be easily controlled by running the reaction below room temperature, terminating it promptly upon completion, and using high-quality NaSH, optimization efforts focused on maximizing throughput, minimizing waste and cycle time, and ensuring that the toluene solution of **7** was suitable for use in the next step. The throughput and waste issues were addressed in a straightforward manner by minimizing the amounts of NaSH, water, and toluene used.

The use of a slight excess (1.1 equiv) of aqueous NaSH ensures fast and complete conversion to product. The use of more NaSH offers no advantage. With enough NaSH and good agitation, the reaction is complete within 1 h after the chlorobutanone addition. Sufficient water is used to prevent the byproduct NaCl from precipitating and thereby interfering with the phase separation.

The optimal toluene usage was governed by the need for a high throughput and short-cycle time process, balanced against the requirement for a high yield. Small amounts of toluene would lead to high throughput and a short distillation time (for recycling toluene), whereas large amounts would allow a faster chlorobutanone feed rate and a more efficient product extraction. Ultimately, the use of about 3 equiv of toluene per equiv of chlorobutanone **6** proved to be an acceptable compromise. The reaction then proceeds in 93−95% yield, and gives a toluene solution containing about 30 wt % of mercaptan **7**.

Scheme 5



An important parameter to be optimized in step 1 was handling the toluene solution of **7**. The subsequent cycloaddition reaction is catalyzed by NaOMe and is sensitive to water and other protic impurities. The amount of water that dissolves in the toluene solution of **7** seems to be tolerated, but any excess, *undissolved* water will cause significant yield losses and processing problems. In the laboratory, after a careful phase separation the toluene solution can be decanted away from any water droplets into a dry reactor for the next step. The cycloaddition proceeds in good yield on material handled this way, although the reaction typically takes longer to initiate (see below). The best results in step 2 are obtained when the toluene solution of **7** is dried with a desiccant, such as Na_2SO_4, molecular sieves, or $CaCl_2$, prior to use.

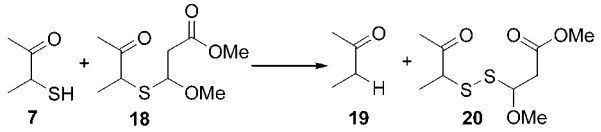
In step 2, the mercaptobutanone (**7**) solution is treated with methyl 3-methoxyacrylate (**11**) in the presence of a catalytic amount of NaOMe. The cyclic product **12** is then treated in situ with concentrated HCl to effect aromatization to ester **13**. The cyclization phase of this step is an equilibrium process as formulated in Scheme 5. The mercaptide anion derived from **7** undergoes conjugate addition to **11** to give the enolate shown, and this partitions between protonation to give **18**, and cyclization to provide, after protonation, cyclic alcohol **12**. Analysis of the reaction composition vs time, in conjunction with control experiments on purified compounds **12** and **18**, indicated that a substantial portion of **12** is formed through direct cyclization of the intermediate ester enolate, without the intervention of **18**, but that most of the **18** that does form is also slowly converted into **12**.[12] Thus, holding the reaction at this stage (after the mercaptan and acrylate are essentially consumed) for some period of time ultimately maximizes the yield, and facilitates purification of thiophene ester **13**.

The major byproducts of the cyclization reaction are the acyclic sulfide **18**, which as mentioned above decreases with increasing reaction time, and surprisingly, 2-butanone (MEK). Although we have no direct evidence, literature precedent[13] suggests that this material could arise by the reaction shown below. According to the proposed mechanism, attack of mercaptobutanone **7**, or the corresponding mercaptide anion,

(11) (a) Coppola, G. M.; Damon, R. E.; Yu, H. *Synlett* **1995**, 1143. (b) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226.
(12) Fevig, T. L.; Phillips, W. G.; Lau, P. H. *J. Org. Chem.* **2001**, *66*, 2493.
(13) Oki, M.; Funakoshi, W.; Nakamura, A. *Bull. Chem. Soc., Jpn.* **1971**, *44*, 828. We thank Börje Björkqvist of Kemira Fine Chemicals for identifying this byproduct.

on the sulfur atom of **18** would give MEK along with unsymmetrical disulfide **20**.

Proposed Mechanism of MEK Formation (ref.13)



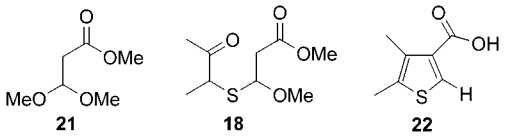
From a practical point of view, this side reaction consumes 2 equiv of mercaptobutanone, resulting in a small yield loss, and perhaps more importantly, produces a volatile byproduct that could accumulate in the recycle toluene stream. A detailed analysis of the reaction showed that MEK production started when the NaOMe was added and stopped once all of the methoxyacrylate was in. We were able to diminish MEK formation somewhat, but never completely, by starting the reaction below room temperature and adding the acrylate in faster. Fortunately, most of the MEK could be removed by distillation, and the low level remaining is well-tolerated in the process.

Aside from temperature and acrylate addition time, other key issues examined included handling of the induction period, stoichiometry, and reaction time. The cyclization is an exothermic reaction and also displays an induction period of variable time, depending mainly on the dryness of the mercaptan solution. Moreover, the order of addition is restricted by the fact that acrylate **11** is destroyed rapidly by alkoxides. Because of these considerations, the following protocol was established. The mercaptobutanone solution is placed in a reactor along with ca. 10% of the total methoxyacrylate charge. The NaOMe is added, and the reaction is monitored for initiation. Once it is clear that the reaction has started, the remaining acrylate is added in at a rate to maintain the desired reaction temperature.

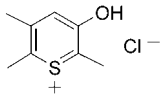
The stoichiometry and reaction time were chosen to maximize conversion of the foul-smelling mercaptan, to minimize usage of the methoxyacrylate, and to simplify purification of the thiophene ester **13**, mainly by minimizing formation of **18**. Relative to 1 equiv of chlorobutanone, the preferred ratios are about 0.1 equiv of NaOMe and ca. 0.94 equiv of acrylate **11**. In the laboratory, it is beneficial to let the reaction run overnight, whereas at the plant, the reaction should be held for as long as possible without creating a new bottleneck in the process. With smaller amounts of NaOMe or **11**, conversion of mercaptobutanone goes down, and the ratio of cyclized product **12** to acyclic sulfide **18** also decreases. Adding significantly more NaOMe improves both the conversion of **7** and the cyclic/acyclic ratio, but also results in an increasing amount of aromatization, and a lower overall yield to be obtained, for reasons that are not fully understood.[14]

In the aromatization phase of step 2, concentrated HCl is added directly to the reaction mixture containing **12**. This results in a 3-phase mixture of an aqueous phase, an organic phase, and precipitated NaCl. At the end of the reaction a minimum amount of water is added to dissolve the salt, and the phases are separated. The organic phase is then washed with $NaHCO_3$ solution, and most of the toluene is distilled from the organic phase through a fractionating column under reduced pressure. The residue is then vacuum distilled through an efficient fractionating column to give high-purity ester **13**.

The principal impurities found after the aromatization are shown below. The dimethoxypropionate **21** is formed by addition of the liberated MeOH to residual acrylate **11**. The acyclic sulfide **18** largely survives the acid treatment, and becomes the most troublesome high-boiling impurity. Carboxylic acid **22** is typically formed in about 1% yield, and is removed with the bicarbonate wash. There is also some tar formation.



A minor, but unusual and unexpected byproduct that formed during the synthesis of **13** and that was isolated during a long-term storage stability test of the compound was identified as hydroxythiopyrylium salt **23**. The isolation and identification of this material is described in the Supporting Information.



Optimization of the aromatization focused primarily on finding the best balance between reaction time and waste load. The reaction requires a strongly acidic medium, but not a stoichiometric amount of acid. If about 0.5−1.0 equiv of concentrated HCl is used, an acceptable reaction time in the desired temperature range is obtained. Unfortunately, the amount of acid used seems to have a much larger effect on the reaction rate than temperature, so that attempts to reduce the HCl charge while increasing the reaction temperature (maintaining the reaction time) were not very fruitful.

The crude product **13** is obtained as a ca. 30 wt % solution in toluene after the reaction workup. To make the process economical, recycling of the toluene was desired. This was accomplished by distilling the volatiles through a fractionating column under reduced pressure; whereupon most of the toluene can be recovered in sufficient purity for recycle. The product is then distilled through a more efficient fractionating column at about 10−50 mmHg. With some recycling of mixed fractions, a ca. 93−95% recovery of **13** can be obtained with a purity of >97%. The isolated yield of **13** from chlorobutanone **6** is therefore about 74%.

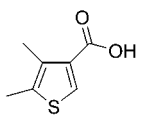
Step 3 is the simple hydrolysis of methyl ester **13** with aqueous LiOH. The reaction was originally done in MeOH, but this cosolvent was later found to be unnecessary. The

(14) It is possible that the water produced during aromatization, after conversion to NaOH by the NaOMe, leads to increased hydrolysis of the ester functionality. With the procedure used at the time this experiment was run, this would not have been seen.

reaction is performed by heating a mixture of the ester and aqueous LiOH at reflux for 1 h. The key parameter in the step is the LiOH charge. Clearly, one equivalent is required to consume the ester, but an overcharge of LiOH may result in greater BuLi usage and will interfere with the Karl Fischer analysis of the dried carboxylate salt and is therefore to be avoided. A pH curve was developed to assess how much LiOH is present after consumption of **13**. In principle, if an unacceptable excess of LiOH is found, more ester can be added.

After the reaction is complete, the lithium carboxylate must be dried prior to treatment with BuLi/diisopropylamine (DIPA). Addition of heptane, followed by azeotropic distillation gives the dry lithium carboxylate as a slurry in heptane. This is then submitted to step 4, wherein the slurry is diluted with THF and treated sequentially with DIPA, *n*-BuLi, and TMS-Cl. The reaction is complete within 1 h after the TMS-Cl addition. THF is then distilled from the mixture through an efficient fractionating column, and can be recycled into the process. The resulting slurry is extracted with water to obtain the lithium carboxylate salt of **4** in the aqueous phase. Acidification with HCl precipitates the product, which is collected by centrifugation and washed with water. The silyl acid **4** (see Scheme 4) is obtained in over 90% yield from ester **13**.

The main identifiable byproducts of the reaction are the unsilylated acid **22**, and the two bis(silylated) acids, **24** and **25**. There is also some tar formation. The amounts of **22** and **24**−**25** formed can be minimized, but never completely suppressed, by adding as close to 1.0 equiv of *n*-BuLi as possible. If this is done, each byproduct is formed in low yield, and they present no significant downstream problems.



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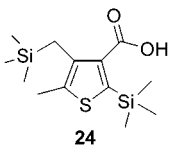

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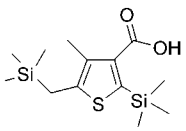

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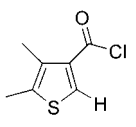
Since the yield is high, and the byproducts can be kept to a minimum as described above, increasing the payload and reducing cycle time became the prime objectives. The payload of the process is limited by the need to use 25% *n*-BuLi/heptane solution, and a relatively large excess of THF to facilitate the metalation and maintain a stirrable slurry at all times. While some improvement in payload can be achieved by using concentrated BuLi solution (85%), the manufacturer's recommendation to keep this material at less than 5 °C and use it promptly to avoid significant degradation made this an impractical solution on large scale. Unfortunately, attempts to use additives such as TMEDA, or solvents other than the expensive THF, were unsuccessful. The only recourse then, was to reduce the THF to a minimum. In this regard, it was helpful to increase the reaction temperature to maintain stirrability. Although in the pilot-plant campaigns the reaction was run at 0 °C, it was later found that it could be done at 20 °C with no significant adverse consequences. At this temperature, the THF usage could be reduced and the batch size could be increased, so that a substantial increase in throughput was realized.

The prime targets for cycle time reduction were the additions of *n*-BuLi and TMS-Cl, both strongly exothermic, and the THF distillation. As mentioned above, running the silylation at 20 °C was found to give acceptable results. This allowed for a much larger temperature differential between the jacket and the batch, and much shorter feed times could therefore be used. The THF distillation is complicated by the presence of *n*-butane (from the BuLi), which must be released carefully. This requires a slow heat-up, so there is little opportunity for cycle time reduction. However, the overall distillation cycle time can be reduced by minimizing THF usage (possible when the reaction is run at 20 °C). Adoption of these changes significantly reduced the overall cycle time for the reaction and THF distillation.

After the THF distillation, the product lithium carboxylate is extracted into water, and the heptane phase is discarded. The aqueous phase at appropriate concentration is acidified by addition of concentrated HCl to precipitate the product. The crude product **4** is then isolated on a centrifuge to afford a wet cake, which can be dried at 50 °C under vacuum. The silylated acid **4** is obtained in 92−94% yield, and generally about 95% purity by this procedure.

In step 5, the dry, silylated carboxylic acid **4** is suspended in hot heptane and treated with thionyl chloride. The solubility of the acid in heptane is very low, but as the $SOCl_2$ is added, all of the solids eventually dissolve to give a solution of the product in heptane. If the reaction is run at high concentration, no catalyst is required and the reaction proceeds rapidly. The process is endothermic overall due to the substantial evaporative cooling from SO_2 and HCl release; therefore, heat must be supplied to maintain the temperature. After the reaction is complete, heating is continued to drive off any remaining HCl and SO_2, and then the excess $SOCl_2$ and heptane are distilled out to leave the high-boiling, liquid acid chloride **15** in the reactor. This is then reconstituted in heptane to the proper concentration for step 6 (see below).

The main byproducts of the reaction are desilylated acid chloride **26** and the anhydride **27**. The anhydride probably always forms in the reaction to some extent, but is slowly converted into the desired acid chloride by the excess of $SOCl_2$ employed. Typically, about 1.2 equiv of $SOCl_2$ are required to drive the reaction to completion. When the level of **27** falls below about 1%, the reaction is terminated since the anhydride will also be converted into silthiofam, and 1% anhydride will result in a yield loss of only 0.5%.



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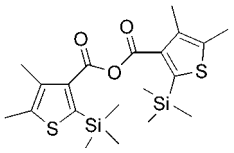

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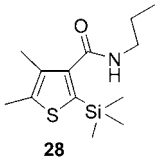
The main issues in step 5 were minimizing desilylation and deciding how to handle the acid chloride. As mentioned above, the desilylation can be managed by performing the reaction in a nonpolar solvent.

The acid chloride proved to have high thermal stability, and could therefore be distilled at vapor temperatures up to 190 °C if desired. By using a fractionating column, the over

silylated materials (acid chlorides corresponding to **24** and **25**), and the desilylated compound **26** could be separated from the desired product **15**. Subsequent processing was thereby improved, and very high-quality silthiofam was obtained by this approach. However, these advantages came at the cost of a 5−10% yield loss, mainly from hold-up in the distilling apparatus, but also due to a small amount of decomposition. It proved more economical overall to simply dilute the crude acid chloride in heptane, filter it, and carry it on to the next step.

In step 6, the filtered heptane solution of the acid chloride is treated with allylamine and aqueous NaOH to produce silthiofam. The concentration of the acid chloride in heptane is chosen to facilitate crystallization of silthiofam at the end. If too little heptane is used, the slurry of final product cannot be transferred to the centrifuge, whereas if too much heptane is used, excessive yield loss to the mother liquor results. The reaction is run under modified Schotten−Baumann conditions. Allylamine is added to the heptane solution of the acid chloride **15** to give partial conversion to product. An aqueous solution of NaOH (1.05 equiv) is then added to finish the reaction, both of these exothermic additions helping to keep the reaction temperature in the desired range. When the reaction is complete, the phases are separated, and the heptane layer is washed with warm water. After the second phase separation, the organic phase is filtered through a small polishing filter to remove a rag layer and cooled to crystallize the product. The silthiofam is collected on a centrifuge, washed with a little cold heptane, and dried under vacuum. The yield of >98% purity material from silyl acid **4** is typically about 85%.

Most of the impurities found in silthiofam result from impurities generated in steps 1−5. For example, allyl amides corresponding to over silylated acids **24** and **25** are found, as well as the allyl amide of desilylated acid **22**. These are the major impurities in isolated silthiofam. Minor impurities generated in the last step include propyl amide **28** derived from propylamine (an impurity in the allylamine), and the imide **29** arising from double acylation of the allylamine. Silyl acid **4** resulting from competing hydrolysis of the acid chloride is also formed to a small extent, and most of what forms is extracted into the aqueous phase. Only a trace of this material, if any, is found in the final product.



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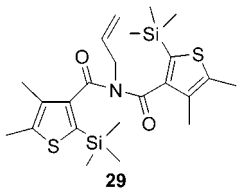

29

The step 6 reaction itself was found to be quite robust. For example, the reaction can be run over a wide temperature range with essentially no change in yield. Also, a variety of reaction solvents and acid scavengers can be used successfully. As mentioned, the use of heptane as the reaction solvent avoids a solvent switch, and it is also a good crystallization solvent for silthiofam. In the original synthesis, a second equivalent of allylamine was used as the acid scavenger, but the cost and toxicity of this material made it an unattractive choice. Triethylamine was also investigated, but offered no advantages and higher cost compared with aqueous NaOH. Despite being a two-phase mixture, with good agitation the reaction is very fast.

Since the reaction is clean, robust, and rapid, ensuring an operationally simple and efficient recovery of high-quality silthiofam became the top priority. Thus, by choosing the crystallization solvent as the reaction solvent and running the reaction at the optimal crystallization concentration, processing is simplified. For the crystallization, a solubility curve of silthiofam in heptane versus temperature was developed. As expected, the lower the temperature, the lower the solubility; however, a target temperature of 0 to −10 °C was finally selected for the crystallization as a balance between cycle time, product recovery, and quality.

The most important variable in the crystallization is the purity of the crude product going in. Even relatively poor-quality silthiofam can upgraded to >98% purity by the recrystallization, but product recovery is greatly diminished because the impurities substantially increase the solubility of silthiofam in heptane. Therefore, since the impurity profile largely depended on the quality of the step 4 product (acid **4**), this step had to be carefully controlled to keep impurities not only low, but also in proper balance.

Conclusions

The process described above now proceeds to give silthiofam in about 60% overall yield from 3-chloro-2-butanone **6**, and is commercially viable. To achieve this result, a novel thiophene synthesis from inexpensive raw materials was developed. Also, a solid isolation was eliminated, and usage of an expensive reagent (*n*-BuLi) was halved by metallating and silylating an in situ-generated lithium carboxylate. Total process solvents were reduced, and solvent switching was minimized, by using toluene and heptane in multiple stages. Desilylation in step 5 was concurrently kept low. Finally, careful control of the silylation reaction allowed a crystallization procedure (for **1**) to be developed that gives reliably formulated silthiofam in high yield and very high purity.

Overall, the process involves isolation of just two intermediates, only one of which is truly purified (distillation of ester **13**), and uses only three organic solvents, all of which can be recycled to a large degree. The process can be run safely and economically on large scale.

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories or Atlantic Microlab. The actual charges of substrates and reagents are given below. The molar amounts are calculated based on the assays of the materials. Similarly, yields are calculated based on assay corrected moles of substrates and products. *Caution! NaSH will react with acid to generate the highly toxic H_2S. Excess NaSH should be oxidized with bleach or hydrogen peroxide prior to disposal. The oxidation is highly exothermic.* The 3-mercapto-2-

butanone is foul smelling, with a very low detection limit. The material should be kept in the fume hood. The 3-chloro-2-butanone is an irritant and lachrymator, and should be handled with due care. Allylamine is highly toxic, volatile (bp 53 °C), and is absorbed readily through the skin; appropriate personal protective equipment should be worn, and the material should be kept in the fume hood.

Methyl 4,5-dimethylthiophene-3-carboxylate (13). A 35-L jacketed reactor equipped with an overhead stirrer, a bottom drain valve, a dropping funnel, a thermocouple and a nitrogen inlet was charged with toluene (6.5 kg), NaSH (43% aqueous solution, 3.43 kg, 26.34 mol), and water (2.72 kg). The mixture was stirred vigorously and cooled to 10 °C. The 3-chloro-2-butanone **6** (2.50 kg, 22.91 mol) was charged through the addition funnel, the reaction temperature being maintained at 15−20 °C by adjusting the feed rate and jacket temperature. The addition required 2 h and 15 min. After the addition was complete, the mixture was stirred vigorously for 1 h while the jacket temperature was raised to 25 °C. Stirring was then stopped, the phases were allowed to separate and settle for 10 min, whereupon the lower, aqueous phase was drained out of the bottom of the reactor. The agitator was pulsed a few times to knock water off the reactor walls and complete the phase separation. *Note: The aqueous phase can be deodorized prior to disposal by treatment with bleach (caution! exothermic reaction)*. After drainage of the aqueous phase, the drain stem was washed with water and acetone, and dried under a stream of nitrogen. The homogeneous, light yellow organic phase containing 3-mercapto-2-butanone **7** was then drained into a tightly sealed polypropylene container while the reactor was cleaned out with water and acetone, and dried under a strong stream of nitrogen.

The solution of **7** (8.75 kg) was then returned to the clean, dry reactor along with a toluene rinse (280 g). A portion of the methyl 3-methoxyacrylate (**11**, 250 g, 2.29 mol) was added to the solution through the dropping funnel, and the mixture was stirred vigorously with the jacket temperature at 15 °C. Solid NaOMe (128 g, 2.29 mol) was added all at once, causing an immediate temperature rise of ca. 3 °C followed by slow cooling of the mixture. After about 30 min, the reaction temperature started rising against the cooling jacket, signaling the initiation of the cyclization. The remaining acrylate (2.28 kg, 19.13 mol) was then added in over 2 h to maintain the reaction temperature below 30 °C. After the addition was completed, the mixture was stirred overnight at room temperature.

The mixture was cooled to 10 °C with good stirring, and concentrated HCl (1.67 kg, 16.93 mol) was added in over about 30 min, producing an exotherm (to 28 °C) and a precipitate of NaCl. The mixture was stirred at room temperature for 1.5 h, and then water (1.39 kg) was added to dissolve the salt. After stirring for 15 min, the phases were allowed to separate and settle for 15 min. The lower, aqueous phase was drained out, and the organic phase containing **13** was washed similarly with 1.98 kg of 5% aqueous $NaHCO_3$. The aqueous phase was drained, and the organic phase was weighed into a small drum. The material weighed 10.59 kg and assayed as 29.8% **13**, indicating a chemical yield of 3.16 kg of **13**, or 81% yield from **6**.

The crude reaction mixture was placed in a 22-L flask equipped with a mechanical stirrer, a vacuum inlet, and a distillation head atop a two-tray, Oldershaw-type, vacuum-jacketed distillation column. Most of the toluene was distilled through the column at ca. 75 mmHg. The residue (6.04 kg) was then transferred to a 6-L flask, similarly equipped, but with a five-tray Oldershaw column. Two early fractions were collected, the first containing mostly toluene, and the second consisting of toluene, acrylate **11**, methyl 3,3-dimethoxypropionate, and **13**. The main fraction of **13** came over at about 109 °C at 11.5 mmHg as a yellow liquid, affording 2.90 kg of material with >99% purity. The isolated yield was therefore 74% from chlorobutanone **6**. The main loss during distillation was in the fraction immediately preceding the main cut. An analytical sample was obtained by washing distilled material with bleach (to oxidize aliphatic sulfur compounds[15]), and redistilling through a Vigreux column under vacuum. The compound was obtained as a nearly colorless liquid, bp 85 °C (3 mmHg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H), 3.80 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 134.3, 134.1, 132.4, 130.1, 51.5, 13.5, 13.4; MS (GC−MS) *m*/*z* 170 (M^+, 54%), 155 (17), 139 (100); Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; S, 18.83. Found: C, 56.37; H, 5.98; S, 18.61.

4,5-Dimethyl-2-trimethylsilylthiophene-3-carboxylic Acid (4). To a 22-L three-necked flask equipped with a thermocouple, condenser, and overhead stirrer under a nitrogen purge was added 1.19 kg (6.57 mol) of ester **13**, and 2.08 kg of a solution of LiOH (6.90 mol) in water. The mixture was heated to reflux for about 60 min, whereupon LC analysis confirmed that the hydrolysis reaction was complete. A Dean−Stark receiver was then placed under the condenser, heptane was added, and the mixture was distilled to the absence of visible water in the distillate. After all methanol and water had been removed, distillation was continued to remove about half of the heptane over about 90 min.

The resulting slurry of the lithium carboxylate was cooled to 0 ± 2 °C, and treated with 4.88 kg of anhydrous, BHT stabilized THF, and 350 g of diisopropylamine (DIPA, 3.42 mol). A solution of *n*-BuLi (1.898 kg, 24.2 wt % *n*-BuLi in heptane, 2.636 L, 7.18 mol) was slowly charged over about 3 h, the long addition time serving solely to maintain the reaction temperature at 0 ± 2 °C. After the addition funnel was rinsed with 50 g of heptane, 797 g (7.26 mol) of chlorotrimethylsilane was added in over 2 h while maintaining the reaction temperature at 0 ± 2 °C. The mixture was stirred for another 30 min, and then assayed by LC to confirm reaction completion.

The reaction mixture was then heated at atmospheric pressure, and the THF (for recycle) was distilled through an efficient fractionating column. The heat-up was performed slowly in order to expel most of the byproduct butane in a controlled manner. After THF distillation, the resulting slurry was cooled to 60 °C, and 1.2 kg of heptane was added. Heating was resumed to distill off 1.2 kg of solvent. The

(15) We thank Dr. James A. Miles for suggesting this procedure.

thick slurry was cooled to room temperature and extracted with two portions of water (8.7 and 7.5 L). The aqueous extracts were combined, cooled to 15−20 °C, and acidified with concentrated HCl to a pH below 4.

The solid product was suction filtered and washed twice with 2 L of cold water to give 2.952 kg of wet cake. The solid was air-dried overnight at 50 °C to afford 1.487 kg (93% assay and 0.2% moisture) of the desired silylated acid **4** as a yellowish-tan solid in 92% yield from ester **13**. An analytical sample was obtained by filtration through a pad of silica gel with hexanes/acetone, 7:1, followed by crystallization from hexanes/acetone. The white crystals melted at 140−142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33(v br s, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 148.4, 139.0, 137.3, 137.2, 14.2, 13.6, 0.1; MS (GC−MS) *m*/*z* 228 (M^+, 5%), 213 (91), 195 (34), 155 (5), 111 (8), 77 (100); Anal. Calcd for $C_{10}H_{16}O_2$-SSi: C, 52.59; H, 7.06; S, 14.04. Found: C, 52.74; H, 7.04; S, 14.08.

4,5-Dimethyl-*N*-(2-propenyl)-2-(trimethylsilyl)thiophene-3-carboxamide (Silthiofam, 1). A 22-L, four-necked flask equipped with an overhead stirrer, dropping funnel, nitrogen inlet, thermocouple, and a condenser was charged with carboxylic acid **4** (956 g, 93% assay, 3.90 mol) and heptane (2.86 kg). The mixture was brought to 75 °C. Thionyl chloride (572 g, 4.81 mol) was added over a period of 30 min via the dropping funnel. Considerable gas evolution (one mole each of HCl and SO_2 per mole of silyl acid) occurred during the addition. After the addition was complete, the gas evolution slowed and finally stopped within 30 min. The gases were trapped in a sodium hydroxide scrubber. The reaction was maintained at 75 °C while a sample was drawn and analyzed by GC. The analysis showed clean, complete conversion of the starting silyl acid to the acid chloride, with no evidence of the lingering intermediate anhydride that is frequently present when the reaction is run on a smaller (50 g) scale.

The reaction mixture was filtered through a sintered glass filter, and the solvents and excess thionyl chloride were removed by distillation under reduced pressure. The acid chloride, a dark brown oil, can be used in the subsequent chemistry without further isolation or purification. Alternatively, the filtration can be done after reconstitution of the crude acid chloride in heptane.

The acid chloride in the 22-L flask was cooled to 60 °C with stirring, and heptane (4.83 kg) was added. Allylamine (220 g, 3.82 mol) was added over a period of 25 min via the dropping funnel, raising the temperature of the reaction mixture from near ambient to 45 °C. Sodium hydroxide (1.56 kg of 10% aqueous solution, 3.90 mol) was added over 20 min via the dropping funnel. The reaction was maintained at 50 °C while a sample was analyzed by GC. The analysis showed complete conversion to the amide product.

Stirring was stopped and the water and heptane layers were allowed to separate. The aqueous layer was drained and the organic phase was washed with 3 L of warm water. The water wash was removed and the organic phase was filtered through a sintered glass filter to remove the small amount of insoluble brown reaction byproducts. The product solution was returned to the 22-L flask and allowed to cool to ambient temperature with stirring. Considerable product crystallized out during this initial cool. The cooling was continued in a cold bath to −2.7 °C. After 10 min at this temperature, the product was filtered on an 18-in. membrane filter and air-dried overnight. Silthiofam (**1**, 916 g corrected for 97.6% assay, 88% yield for the two steps) was recovered as light tan needles. An analytical sample was prepared by filtration through a pad of silica gel (hexanes/acetone, 10:1), followed by recrystallization from hexanes to give white needles, mp 87.5−89 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.95−5.84 (m, 1H), 5.65 (br s, 1H), 5.23 (apparent dq, J = 17.2, 1.5 Hz, 1H), 5.15 (apparent dq, J = 10.2, 1.2 Hz, 1H), 4.01 (apparent tt, J = 5.8, 1.4 Hz, 2H), 2.30 (s, 3H), 2.12 (s, 3H), 0.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 145.6, 139.5, 135.5, 134.0, 133.2, 117.4, 42.5, 13.5, 12.8, 0.3; MS (GC−MS) *m*/*z* 267 (M^+, 1%), 252 (100), 211 (13), 194 (7); Anal. Calcd for $C_{13}H_{21}NOSSi$: C, 58.38; H, 7.91; N, 5.24; S, 11.99. Found: C, 58.18; H, 8.08; N, 5.32; S, 12.03.

Acknowledgment

We thank Tony Yang, Ming Zeng, and Dorothy Honda for isolating many of the impurities, and Lydia Swenton and Jan Gard for their help in identifying them. We also gratefully acknowledge engineering support from David Addison, Jim Jones, Kim Kolbert, Brent Massmann, Randy Meyer, and Mike Suda. Stephanie Camden, Jung-Min Park, Erwin Irdam, Shan Lin, and Tony Thompson provided safety data and/or consultation. Finally, we thank Rich Wettach, Sai Wong, and Dennis Phillion for their early contributions and helpful discussions, Ray Frame for help with the scale-ups, and Bill Miller for advice on the manuscript.

Note Added after ASAP: The uncorrected version was posted ASAP May 10, 2002. The corrected version was posted June 5, 2002.

Supporting Information Available

Experimental procedures for the isolation, identification, and reduction of thiopyrylium salt **23**; ^{1}H and ^{13}C NMR and UV spectra of **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review February 18, 2002.

OP020206F