A Practical Synthesis of a COX-2-Specific Inhibitor

Ian W. Davies,* Jean-Francois Marcoux, Edward G. Corley, Michel Journet, Dong-Wei Cai, Michael Palucki, Jimmy Wu, Robert D. Larsen, Kai Rossen, Philip J. Pye, Lisa DiMichele, Peter Dormer, and Paul J. Reider

Department of Process Research, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065

ian_davies1@merck.com

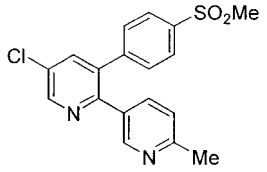
Received June 7, 2000

A number of synthetic strategies to the Cox-2 specific inhibitor **1** have been described. These studies have led to the identification of a novel pyridine construction using annulation of ketone **2** using a vinamidinium species **29** and ammonia in 97% assay yield. Three approaches to the synthesis of ketone **2** are described that allow for its preparation in large quantities in >65% overall yield from methyl 6-methylnicotinate.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) used for the treatment of inflammatory conditions act by inhibition of cyclooxygenase (COX), the first enzyme involved in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid. The major COX isozyme, COX-1, is expressed as a constitutive enzyme and is involved in homeostasis of the gastrointestinal (GI) tract (in addition to other functions).[1] The discovery[2] of an inducible COX isozyme, commonly referred to as COX-2 and expressed principally in inflammatory tissue, has led several groups to search for selective inhibitors of COX-2.[3] The rationale behind these investigations is that a specific COX-2 inhibitor will greatly improve the side-effect profile, including gastric ulceration, that is commonly associated with the chronic use of traditional NSAIDs. Recently, a series of novel 2-pyridinyl-3-(4-methylsulfonyl)phenylpyridines has been evaluated by Merck for their ability to inhibit the isozymes of cyclooxygenase, COX-1, and COX-2. Optimal COX-2 inhibition was observed by introduction of a substituent at C5 of the central pyridine. 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine **1** was identified as a very potent and specific COX-2 inhibitor that may provide therapeutically useful alternatives to traditional NSAIDs with a greater GI safety profile.[3]

Previous synthetic strategies to these diaryl pyridines have employed transition metal cross-coupling—Suzuki or Stille—of preformed pyridines and were very effective at preparing a wide range of substrates for preliminary biological evaluation.[3] With the identification of **1** as a development candidate, a more focused synthetic approach was initiated. We envisioned that these compounds may be assembled by construction of the central pyridine ring (Scheme 1) with the introduction of the C-5 substituent in a single step. This disconnection would lead to ketone **2**, a three-carbon annulating agent **3**, and ammonia.



1

Previously, the efficient construction of trisubstituted pyridines via the annulation of ketones with vinamidinium salts was described in a Letter.[4] In this paper, a number of synthetic approaches to the ketosulfone **2** and full details of the development of the efficient practical annulation strategy for the construction of the central pyridine ring are disclosed.

Results and Discussion

Approaches to Ketosulfone 2. Three of the approaches that have been examined are outlined below and have relied on the construction of the central C−C single bond of the ketosulfone. Our strategy has required the use of a preformed 6-methyl-substituted pyridine ring, and with the ready availability from the Lonza nicotinamide process, methyl 6-methyl nicotinate **4** was the most obvious choice of starting material.[5] Two approaches directly involve the 6-methylnicotinate as an electrophilic component whereas the third uses the 6-methylpyridine as nucleophilic component after appropriate derivatization.

(1) Horner−Wittig Approach. This approach relies on the modified Horner−Wittig reaction developed by Zimmer.[6] Coupling of the N,P-acetal **6** and the commercially available 4-methanesulfonylbenzaldehyde gen-

* Corresponding author. Tel: 732 594 3174. Fax: 732 594 1499.

(1) For a review see: Griswold, D. E.; Adams, J. L. *Med. Res. Rev.* **1996**, *16*, 181.

(2) (a) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erickson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692. (b) Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. *J. Biol. Chem.* **1991**, *226*, 2692. (c) Masferrer, J. L.; Seibert, K.; Zweifel, B.; Neddleham, P. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 3917. (d) Hla, T.; Neilson, K. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7384.

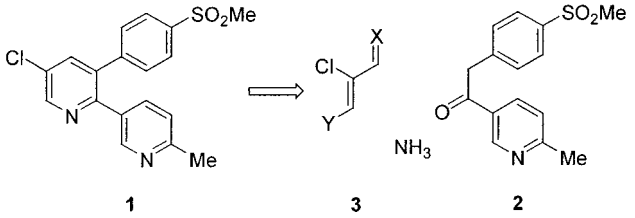
(3) Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, J. L.; Young, R. N. *Bioorg. Med. Lett.* **1998**, *8*, 2777.

(4) Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339.

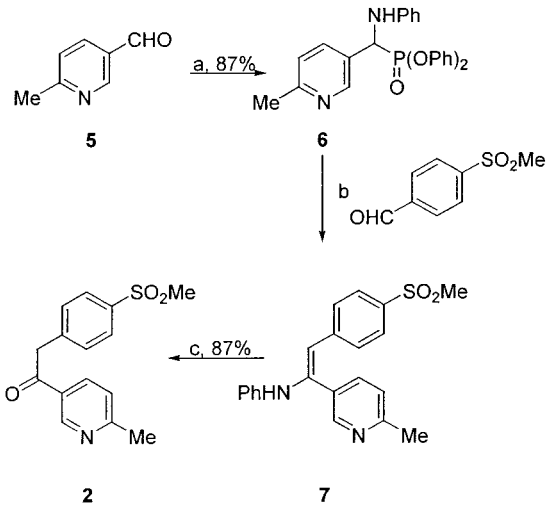
(5) Grayson, J. I. EP 0128279A2, 1984.

10.1021/jo000870z CCC: $19.00
Published on Web 09/19/2000

Scheme 1



Scheme 2[a]

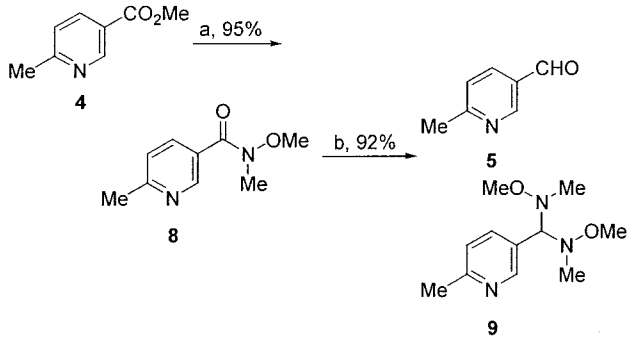


[a] Reagents: (a) aniline, diphenyl phosphite, IPAC; (b) potassium *tert*-butoxide, IPA/THF; (c) 2 N HCl.

erates the enamine **7** which after hydrolysis leads to the desired ketosulfone **2** (Scheme 2). The N,P-acetal is derived from the nicotinaldehyde **5**, and in order for this approach to be successful a straightforward synthesis of this aldehyde was required.

For initial probe experiments the 6-methyl methylnicotinate **4** was reduced to the alcohol using LAH and oxidized to the aldehyde **5** using MnO_2 in 91% overall yield.[7] This pathway was not suitable for large scale production of **5**. Reduction of the ester **4** using 1 equiv of DIBAL-H in methylene chloride, toluene, or ethereal solvents led to clean formation of the alcohol in 50% conversion independent of the order of addition or quench method used. With the propensity for over-reduction of the ester, the reactivity of the Weinreb amide **8** was investigated. The direct conversion of esters to their Weinreb amides has previously been described by Williams.[8] In the published procedure, a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride and appropriate ester in THF was treated with isopropylmagnesium chloride followed by aqueous ammonium chloride quench to give the Weinreb amide in high yield. Slight modifications were introduced to make this procedure more efficient. By reaction of 1.6 equiv of *N*,*O*-dimethylhydroxylamine as the free-base in toluene at <−7 °C, 1.4 equiv of isopropylmagnesium chloride could be used in place of the 2.8 equiv required for the HCl salt. The presence of byproducts resulting from *i*-PrMgCl addition

Scheme 3[a]



[a] Reagents: (a) HNMe(OMe), i-PrMgCl, toluene; (b) DIBAL-H, toluene.

to the pyridine, ester, or Weinreb amide were minimized to <0.1% under these conditions. The replacement of tetrahydrofuran by toluene aided extractions during isolation and allowed for the introduction of a through process. The reaction was quenched into 1 equiv of 10% aqueous acetic acid which proved to be an excellent system for extraction of the magnesium salts since $Mg(OAc)_2$ is a very soluble salt (390 g/L) in contrast to the complex $(NH_4)MgCl_3$ which has low solubility.[9] The pH of the quench is also weakly acidic and avoids the precipitation of magnesium hydroxide. With these modifications the Weinreb amide was obtained as a 25 wt % solution in toluene in >95% yield (Scheme 3).

Reduction of the intermediate Weinreb amide **8** was achieved in toluene using 20 wt % DIBAL-H at <−15 °C to give the aldehyde **5** in 92% yield. The reaction was accompanied by <5% over-reduction. Isolation of the aldehyde was achieved by quenching excess reagent with 1 equiv of ethyl acetate and workup using aqueous (L)-tartaric acid. This procedure led to isolation of the desired aldehyde with varying amounts of the aminal **9**, which could be used in the next step without complication. The solution of aldehyde **5** was solvent switched to a 30 wt % solution in IPAC for use in the next step.

Since the N,P-acetal **6** is the first crystalline intermediate in the synthesis, it was important that impurities from the previous steps were adequately rejected. After much experimentation, the optimal solvent for isolation of the N,P-acetal was isopropyl acetate/*n*-heptane. This led to the selection of IPAC as the solvent for the acetal formation. Treatment of a solution of the aldehyde in IPAC with 1.2 equiv of aniline at 60 °C led to the formation of the intermediate imine. The aminal **9** was also converted to the imine under these conditions. Addition of 1.7 equiv of technical grade diphenyl phosphite (~85% phosphite, ~15% phenol) over 30 min at 60−65 °C formed the N,P acetal in >92% assay yield. The reaction mixture was seeded with **6** and the product crystallized by the addition of 1.1 volumes of *n*-heptane over 2 h followed by cooling to 15 °C. The crystalline N,P-acetal was isolated by filtration in >99A% by HPLC in 87% isolated yield. The control of the aniline and phenol levels in the N,P-acetal were critical to ensure the yield and quality of ketosulfone obtained in the next step.

A wide range of bases, solvents and temperatures were examined for the conversion of N,P-acetal **6** to ketosulfone **2**. The original conditions reported for the reaction

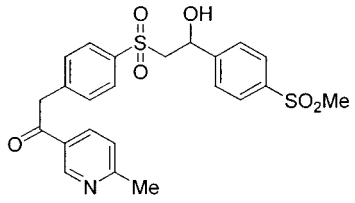
(6) (a) Zimmer, H.; Bercz, J. P. *Justus Liebigs Ann. Chem.* **1965**, *686*, 107−114. (b) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008−4017.

(7) Nishikawa, Y.; Shindo, T.; Ishii, K.; Nakamura, H.; Kon, T.; Uno, H. *J. Med. Chem.* **1989**, *32*, 583.

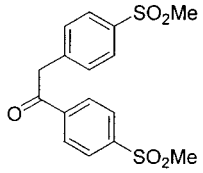
(8) Williams, M. J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(9) Seidell, A *Solubilities of Inorganic and Metal Organic Compound*; Van Nostrand: New York, 1940.

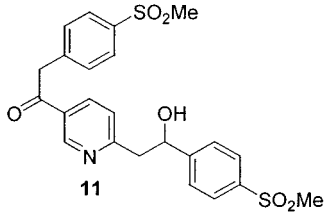
by Zimmer[5] utilized methanol/KOH at −40 °C which we have already reported can lead to a significant side reaction via saponification of the phosphonate.[10] The use of $CsCO_3$ in THF/IPA followed by HCl hydrolyis of the enamine led to a smooth reaction to give ketosulfone in 85% isolated yield. However this procedure requires the reaction of an excess of the insoluble $CsCO_3$ with the N,P-acetal which in turn is coupled with a sparingly soluble aldehyde. The reaction rate was shown to be a function of the particle size of the cesium carbonate. This procedure was troublesome upon scaleup. An additional problem was the generation of the alcohol impurities **10** and **11** at up to 1 A%. The bis-sulfone impurity **12** was also present in up to 0.5 A%. These ketone impurities carried



10



12



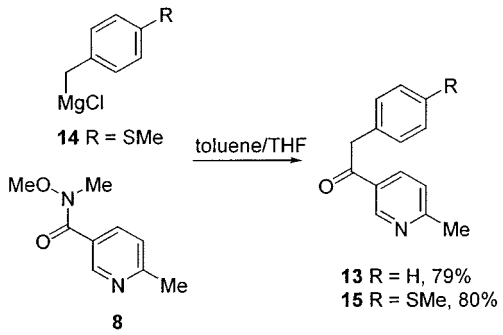
11

forward to pyridines in the annulation reaction with essentially quantitative conversion and were difficult to reject thus compromising the purity of **1**. For this reason a method to minimize their formation in the ketosulfone step was investigated. Optimal conditions involved addition of 1.05 equiv of potassium *tert*-butoxide over 1 h to a slurry of N,P-acetal in THF/IPA (0.7:1) at 25 °C. The enamine intermediate was hydrolyzed by addition of 4 equiv of 2 N HCl to give the ketosulfone in 94% assay yield. The formation of the alcohol impurities was essentially inhibited under these conditions. The ketosulfone product was isolated by adjusting the pH of the solution to ~5.5 with 5 N NaOH at 45 °C. The ketosulfone was isolated by filtration following cooling to −10 °C and washing with IPA/water (1:1) to give an 87% isolated yield of **2** with >99 A% purity by HPLC.

The Horner−Wittig strategy led to generation of ketosulfone in four steps and 65% overall yield from methyl 6-methylnicotinate **4**.

(2) Grignard Approach. Since the Weinreb amide **8** is an intermediate in the synthesis of nicotinaldehye **5**, addition of a nucleophilic organometallic reagent to **8** might provide direct access to the ketosulfone.

The use of 4-thiomethylbenzylmagnesium chloride **14**, derived from the chloride in diethyl ether, has been employed by this group as an intermediate in the synthesis of Clinoril.[11] Reaction of a 2 M solution of the Grignard **14** in ether with the Weinreb amide in toluene led to the ketone in 82% isolated yield. To avoid the use of diethyl ether in the Grignard formation, a variety of solvents were screened. In our hands, the use of THF led to almost exclusive formation of the ethane dimer **16**,[12] while the use of other ethereal solvents[13] failed to give any Grignard formation. However, similar results to those using diethyl ether were obtained by preparing the Grignard reagent in toluene using 1.5 equiv of magnesium and addition of the chloride dissolved in 2 equiv of tetrahydrofuran at <35 °C. Addition of the Grignard reagent (after decanting off the excess magnesium) to the Weinreb amide at <−15 °C gave the ketosulfide **15** in 80% isolated yield at 1 mol scale.



Oxidation of the sulfide **15** to ketosulfone **2** was achieved very effectively using Oxone in ethyl acetate.[14] However, due to the polarity of the ketosulfone, it proved difficult to obtain a pure sample free of inorganics. Oxidation using acetic acid/hydrogen peroxide at 100 °C was very sluggish. Tungstate-catalyzed oxidation proved to be effective in ODCB or methanol using aqueous hydrogen peroxide as the stoichiometric oxidant. Oxidation of the ketosulfide in the presence of sulfuric acid at 60 °C minimized the formation of *N*-oxide **17** to <0.3 A% via in situ protection of the pyridine. Ketosulfoxide **18** was readily isolable at incomplete conversion. Methanesulfonic acid can also be used in place of sulfuric acid. An excess of hydrogen peroxide was required to drive the reaction to completion due to a competitive oxidation of methanol under these conditions. The ketosulfone was isolated in 89% yield by filtration after cooling to ambient and washing with water.

The Grignard/oxidation route afforded ketosulfone **2** in three step and 68% overall yield from methyl 6-methyllnicotinate **4**.

(3) Claisen Approach. An alternative construction of ketosulfone **2**, again relying on the nicotinate **4** as the source of the pyridine, utilizes a Claisen condensation of **4** with **20** or **21**. The substituted phenyl acetic acid **20** or ethyl ester **21** as the required nucleophilic partner have been previously described.[14] However, due to the ready availability of the ketone **19**, the acid **20** was conveniently prepared using the Willgerodt−Kindler reaction.[16] The

(10) Journet, M.; Cai, D.-W.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*,1717.

(11) Pines, S. H.; Czaja, R. F.; Abrahamson, N. L.. *J. Org. Chem.* **1975**, *40*, 1920.

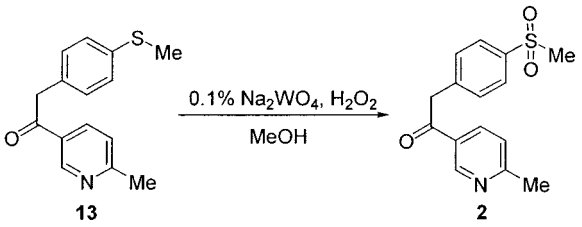
(12) This is in contrast to a literature report where coupling with *N*-methyl-3,4-lutidinium iodide was reported to occur in THF with a crude yield of 44%: Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujimura, H.; Nozaki, M.; Niwa, M. *J. Med. Chem.* **1985**, *28*, 1660.

(13) Jones, R. V. H.; Ewins, R. C.; Mellor, R. M. US 5,242,625, 1993.

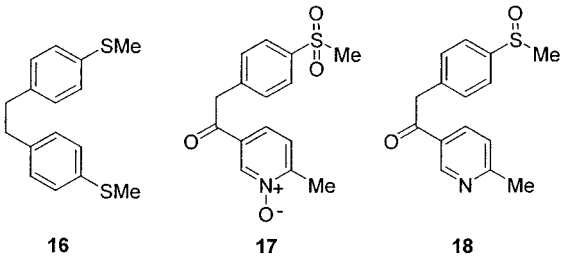
(14) For tungstate oxidation of a related COX-2 inhibitor, see: Tan, L.; Chen, C.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3961. For Oxone oxidation of a related Cox-2 inhibitor see: Xu, F.; Zhao, D.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron* **1999**, *55*, 6001.

(15) Forrest, H. S.; Fuller, A. T.; Walker J. *J. Chem. Soc.* **1948**, 1501. Forrest, H. S.; Fuller, A. T.; Walker J. *J. Chem. Soc.* **1948**, 1504.

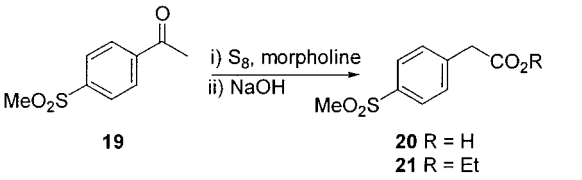
(16) Willgerodt, C. *Chem. Ber.* **1887**, *20*, 2467. Willgerodt, C. *Chem. Ber.* **1888**, *21*, 534. Kindler, K. *Liebig's Annalen* **1923**, *431*, 193.



(2)

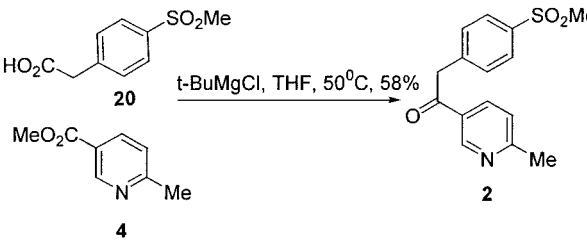


acid was obtained in 57% yield, and the ester **21** was prepared using Fischer esterification in 99% yield.



(3)

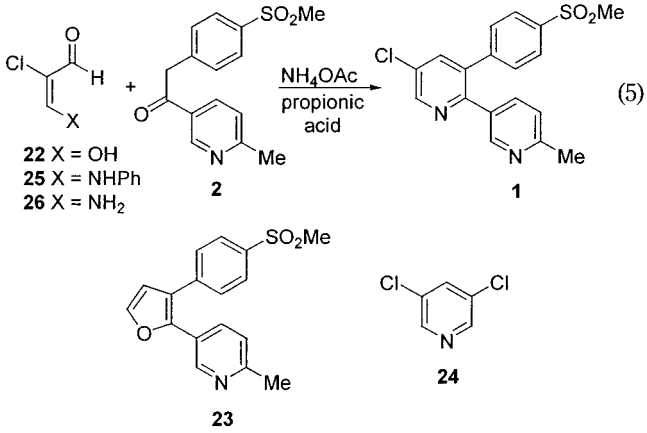
Reaction of the ester **21** with methyl nicotinate **4** using potassium *tert*-butoxide in *tert*-butyl alcohol as base followed by acid hydrolysis/decarboxylation only led to small amounts of the desired ketsoulfone **2**. This was presumably due to the ease of retro-reaction in this system. The use of Ivanoff conditions, i.e., the magnesium dianion in THF (formed using 2 equiv of *tert*-butylmagnesium chloride) at 50 °C proved to be more successful; however, in this case the conversion was limited to < 50%. This problem was overcome by the addition of an extra 1 equiv of *tert*-butyl magnesium chloride during the course of the reaction. Therefore, by using a total of 3 equiv of *tert*-butylmagnesium chloride the ketosulfone **2** could be obtained in 58% yield directly from nicotinate **4**.



(4)

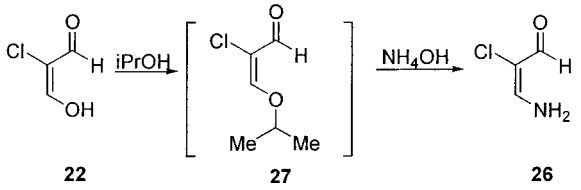
Pyridine Annulation of Ketosulfone. The key disconnection in the synthesis of **1** that we wished to exploit was the annulation of ketosulfone **2** with an appropriate three-carbon synthon **3** and ammonia (Scheme 1). Two broad classes of reaction have been investigated using acid- or base-induced enolization of the ketosulfone and subsequent reaction with a derivative of chloromalonaldehyde **22**.

Acid-Promoted Annulation/Friedlander Condensation.[17] When a mixture of chloromalonaldehyde (3 equiv),[18] **22**, ammonium acetate (9 equiv), and ketosulfone **2** were heated with propionic acid at 125 °C, pyridine **1** was produced in 62% assay yield together with a the furan impurity **23** in 15% assay yield. Isolation by chromatography led to the desired pyridine **1** in 49% yield and the furan **23** in 11% yield. In addition to the furan, the 3,5-dichloropyridine **24** was observed in up to 5% assay yield. The generation of these two impurities suggests that decarbonylation of a chloromalonaldehyde derivative is a significant reaction pathway under these conditions. The reaction of aniline derivative **25**, an isolable intermediate in the Dieckmann synthesis of chloromalonaldehyde, behaved similarly in the reaction to give the pyridine **1** in 47% assay yield.



(5)

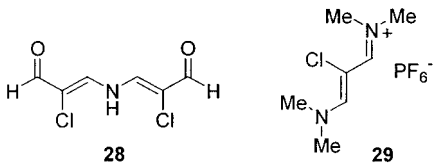
Careful monitoring by HPLC indicated that aminoacrolein **26** was an intermediate in the reaction. The aminoacrolein was conveniently prepared from the vinylogous isopropyl ester **27** in 80% overall yield starting with chloromalonaldehyde. When the annulation reaction was performed with the isolated aminoacrolein in the absence of ammonium acetate, the level of furan **23** was significantly reduced to <5%. Four equivalents of aminoacrolein was still required to drive the reaction to completion. By addition of a strong acid the formation of the furan could be further minimized. Optimal conditions utilized 2 equiv of methanesulfonic acid in a mixture of toluene/propionic acid where the levels of furan could be reduced to <1% with 72% assay yield. However, the reaction was still plagued by large amounts of polymeric material and suffered from the serious disadvantage that an excess of aminoacrolein was required. Further study revealed that the reaction of aminoacrolein to form the head-to-head dimer **28** was a competing side reaction under these conditions. While kilogram quantities of pyridine **1** could be prepared with this approach, it was



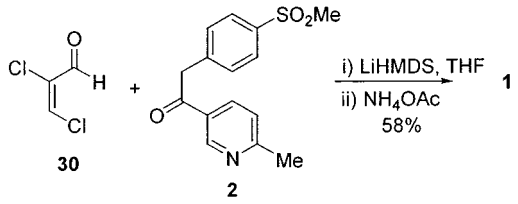
(17) Breitmaier, E.; Bayer, E., *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 765.

(18) Dieckmann, W.; Platz, L. *Ber. Deut. Chem. Ges.* **1904**, *37*, 4638. Chloromalonaldehyde is commercially available from PPG Industries.

apparent that a more efficient process was required for the production of even larger amounts of **1**.[19]



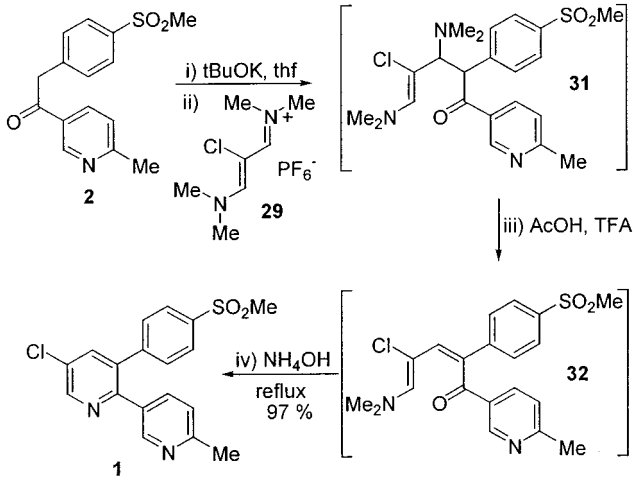
(2) Base-Promoted Annulation. Alternatively reaction of the enolate of ketone **2** with a variety of three carbon electrophiles was examined. 2,3-Dichloroacrolein **30**[20] was prepared by treatment of chloromalonaldehyde with oxalyl chloride in toluene and catalytic DMF followed by distillation in 80% yield. Reaction of the lithium enolate of ketosulfone with dichloroacrolein **30** in THF followed by reaction with ammonim acetate or anhydrous ammonia at reflux led to the formation of pyridine **1** in up to 58% assay yield. The reaction could not be optimized further, and this approach was discontinued due to expected difficulty in handling dichloroacrolein at large scale.



Vinamidinium salts have been used in the synthesis of nitrogen-containing heterocycles, e.g., pyrroles and pyrimidines. Carbonyl enolates are known to add to vinamidinium salts to produce dienaminones,[21] and enolates of substituted aryl methyl ketones are alkylated by vinamidinium salts.[22] In the latter case the formation of pyridine rings was achieved in a three-step process in 36−46% yield via the formation of the corresponding pyrylium salts and reaction with ammonium acetate. We have described the preparation of several vinamidinium hexafluorophosphate salts and recently reported that these salts are suitable three-carbon synthons that react with ketone enolates to form 2,5-disubstituted-3-arylpyridines in good to excellent yield.[4]

To this end 2-chloro-*N*,*N*-dimethylaminotrimethinium hexafluorophosphate salt **29**[23] (1.05 equiv) was reacted with ketone **2** (1.00 equiv) in the presence of an equimolar amount of *t*-BuOK in THF at ambient temperature (Scheme 4). Inverse quench of the resulting adduct **31** into a mixture of 7 equiv of HOAc and 0.75 equiv of TFA in THF at <30 °C led to the putative intermediate **32**. Ring closure of the pyridine ring occurred upon heating at reflux in the presence of an excess of aqueous ammonium hydroxide to give the pyridine **1** in 97% assay yield. Replacement of the potassium base with sodium

Scheme 4



tert-butoxide or LDA decreased the yields significantly and resulted in the recovery of large quantities of unreacted ketosulfone. The desired pyridine **1** was isolated in 94% yield following chromatography. The pK_a of **1** was determined to be 4.5[24] making it more convenient on a large scale to isolate the pyridine as the *p*-toluenesulfonic acid salt in 91% yield without resorting to chromatography.

Summary

We have described syntheses which allow for the preparation of **1** in four or five steps with >60% overall yield from methyl 6-methylnicotinate. These studies have resulted in the discovery of a novel pyridine construction involving the annulation of ketosulfone and CDT-phosphate. This reaction has significant advantages over more traditional acid-promoted reactions and should provide broad applicability for the synthesis of substituted pyridines.

Experimental Section

Melting points were determined are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Water content was determined by Karl Fischer titration.

1-(6-Methyl-3-pyridinyl)-1-(aminophenyl)methanodiphenylphosphonic Acid 6. To a solution of methyl 6-methylnicotinate (21.56 g, 0.143 mol) and *N*,*O*-dimethylhydroxylamine (13.90 g, 0.30 mol) in toluene (150 mL) at −10 °C was added isopropylmagnesium chloride (110 mL, 2 M in THF) over 2.5 h. The reaction mixture was aged for 30 min and then transferred to 10% aqueous acetic acid (126 mL) at 5 °C. The layers were separated, and the aqueous layer was extracted with toluene (×2). The layers were concentrated with the concomitant addition of toluene to reduce the KF to <200 μg/mL to give a ∼30 wt % solution of **8** in toluene. The solution was cooled to − 20 °C and DIBAL-H (99 mL, 1.5 M in toluene, 1.1 equiv) was added over 30 min allowing the temperature to reach −5 °C over the course of the addition. Excess reagent was quenched by the addition of ethyl acetate (15 mL). The reaction is aged for 30 min at −10 °C to 0 °C and then added to a 20% tartaric acid solution maintaining the temperature <30 °C. The mixture is aged for 1 h at 20−25 °C with efficient

(19) One further acid-promoted approach was briefly investigated. Reaction of the vinamidinium salt **29** with the ketone **2** using propionic acid as solvent in the presence of ammonium acetate at 100 °C led to the formation of pyridine in 30% assay yield. Further optimization of this reaction was not undertaken due to the success of a related base-promoted reaction.

(20) Jaehnisch, K.; Duczek, W. Synthesis **1992**, *10*. 935. Jaehnisch, K.; Seeboth, H.; Duczek, W. *Chem. Abstr. 88*, 492278. Patent Appl. DD 86-294822. Brackeen, M.; Howard, H. R. EP 0352959.

(21) Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 4759.

(22) Pavlyuchenko, A. I.; Smirnova, N. I.; Kovshev, E. I. *Khim. Geterotsikl. Soedin.* **1985**, *10*, 1392.

(23) Davies, I. W.; Marcoux, J.-F.; Wu, J.; Corley, E. G.; Robbins, M. A.; Palucki, M.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571.

(24) pK_a was measured in a range of methanol/water mixtures and extrapolated to 100% water.

stirring. The pH is adjusted to 8.0 with 50% sodium hydroxide, and the mixture is aged with stirring for 30 min. The layers are separated, and the aqueous layer is extracted with isopropyl acetate. The organic layers are concentrated successively with the concomitant addition of IPAC to give a ~30 wt % solution aldehdye **5** with KF < 200 μg/mL. IPAC (160 mL) and aniline (12.8 g, 0.137 mol) were added, and the mixture was heated to 60 °C. Diphenyl phosphite (60 g, 86 wt % technical grade, 0.212 mol) was added over 1 h. The mixture was seeded with N,P-acetal **6**, and heptane (180 mL) was added over 1 h. The mixture was cooled to 15 °C, and the product isolated by filtration. The cake was slurry washed with water followed by IPAC/heptane (1:1) and dried to give N,P-acetal as a colorless solid (46.5 g) in 76% yield: mp 135−137 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.69 (t, 1H, J = 2.3 Hz), 7.26 (m, 4H), 7.15 (m, 7H), 6.98 (m, 2H), 6.77 (t, 1H, J = 7.4 Hz), 6.64 (dd, 2H, J_1=8.6 Hz, J_2=0.9 Hz), 5.17 (d, 1H, J = 24.7 Hz), 4.89−5.09 (br, 1H), 2.55 (d, 3H, J = 2.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) L 158.4, 158.3, 150.2, 150.1, 150.0, 149.9, 148.7, 148.7, 145.4, 145.2, 136.0, 135.9, 129.7, 129.7, 129.4, 129.3, 128.0, 125.50 125.3, 123.5, 123.5, 120.5, 120.5, 120.2, 120.1, 119.2, 115.5, 114.0, 54.2, 52.7, 23.9. Anal. Calcd for $C_{25}H_{23}N_2O_3P$: C, 69.8; H, 5.4; N, 6.5. Found: C, 69.8; H, 5.2; N, 6.3.

1-(6-Methyl-3-pyridinyl)-2-[4-(methylsulfonyl)phenyl]-ethanone 2. Procedure A: To a suspension of N,P-acetal **6** (44.38 g, 0.100 mol) and sulfonylbenzaldehyde (22.14 g, 0.113 mol) in tetrahydrofuran (150 mL) and isopropyl alcohol (300 mL) at 25 °C was added dropwise potassium *tert*-butoxide (71 mL, 1.6 M in THF, 0.113 mol) over 2 h. The resulting solution was aged 30 min and was treated with 2 N HCl (200 mL). The homogeneous reaction mixture was aged 1 h and was heated to 45 °C. Sodium hydroxide (5 N) was added dropwise to the reaction mixture (71 mL) to pH 5.0−5.3. The reaction mixture was aged 1 h at 45 °C and cooled to −15 °C over 3 h. The product was filtered, and the cake was washed with cold IPA/water (1:1) and water and dried by a nitrogen sweep to give ketosulfone **2** (24.91 g) as an off-white solid in 86% isolated yield.

Procedure B: To a solution of sulfide **15** (270 g, 1.05 mol) and sulfuric acid (2 N, 20 mL) in methanol (2700 mL) at 55 °C was added a solution of sodium tungstate (6.0 g, 0.02 mol) in water (200 mL). Hydrogen peroxide (380 mL, 30% aq) was added over 2 h. Water (3000 mL) was added over 0.5 h, and the mixture was cooled to ambient. The product was isolated by filtration, washed with water, and dried to give ketosulfone **2** as a colorless solid (269 g) in 89% isolated yield. DSC peak 185.6 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 9.10 (s, 1H), 8.15 (dd, 1H, J_1=8.1 Hz, J_2=2.3 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.3 Hz), 7.28 (d, 1H, J = 8.1 Hz), 4.37 (s, 2H), 3.03 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) L 194.8, 163.9, 149.4, 140.1, 139.3, 136.0, 130.6, 129.0, 127.6, 123.4, 45.1, 44.4, 24.7. Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.27; H, 5.17; N, 4.74.

1-(4-(Methylsulfonyl)phenyl) 2-[4-(methylsulfonyl)-phenyl]ethanone 12: mp 151−153 °C; ^{1}H NMR (300 MHz, d_6-DMSO) L 8.29 (d, J = 8 Hz, 2H), 8.10 (d, J = 8 Hz, 2H), 7.89 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 2H), 4.67 (s, 2H), 3.30 (s, 3H), 3.22 (s, 3H). Anal. Calcd for $C_{16}H_{16}O_5S_2$: C, 54.53; H, 4.58. Found: C, 54.95; H, 4.58.

1-(6-Methyl-3-pyridinyl)-2-[4-(methyl sulfide)phenyl]-ethanone 15. To a slurry of magnesium turnings (191 g, 7.86 mol) in toluene (4 L) was added a solution of 4-thiomethylbenzyl chloride (566 g, 3.28 mol) in THF (0.545 L, 6.73 mol), maintaining the temperature below 36 °C. The Grignard solution is transferred to a solution of Weinreb amide (300 g, 1.66 mol) in toluene (1.7 L), maintaining the temperature below − 10 °C. The mixture was aged for 1 h and then quenched by the addition of aqueous acetic acid (50 wt %, 0.5 L). Toluene and water were added and the layers separated. The aqueous layer was extracted with toluene (×2) and concentrated to a yellow solid. Recrystallization from isopropyl acetate/heptane (9 L) gave the ketosulfide as a colorless solid (342 g) in 80% isolated yield: mp 111−113 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 9.09 (d, 1H, J = 1.6 Hz), 8.12 (dd, 1H, J_1=8.1 Hz, J_2=2.3 Hz), 7.2 (m, 5H), 4.21 (s, 2H), 2.60 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 196.0, 163.3, 149.6, 137.2, 136.1, 130.5, 129.8, 129.2, 127.0, 123.3, 45.1, 24.7, 15.8. Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44. Found: C, 69.96; H, 5.82; N, 5.37.

1-(6-Methyl-1-oxido-3-pyridinyl)-2-[4-(methylsulfonyl)-phenyl]ethanone 17: mp 180−183 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.85 (s, 1H), 7.92 (d, 2H, J = 8.3 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.42 (m, 3H), 4.33 (s, 2H), 3.05 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 192.5, 153.7, 139.7, 139.5, 139.0, 132.7, 130.6, 127.8, 126.5, 124.3, 45.1, 44.4, 18.03. Anal. Calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 59.11; H, 4.98; N, 4.52.

1-(6-methyl-3-pyridinyl)-2-[4-(methylsulfinyl)phenyl]-ethanone 18: mp 133−134 °C;^{1}H NMR (400 MHz $CDCl_3$) δ 9.12 (s, 1H), 8.16 (dd, 1H, J_1=8.1 Hz, J_2=2.0 Hz), 7.62 (d, 2H, J = 8.1 Hz), 7.43 (d, 2H, J = 8.1), 7.28 (d, 1H, 8.3 Hz), 4.34 (s, 2H), 2.71 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 195.3, 163.7, 149.4, 144.53, 137.0, 136.1, 130.5, 123.9, 123.4, 45.1, 43.8, 24.7. HRMS Found: 273.10, Calcd for $C_{15}H_{15}NO_2S$: 273.08.

5-Chloro-3-(4-methanesulfonylphenyl)-6′-methyl[2,3′]-bipyridinyl 1. To a suspension of ketosulfone 2 (7.24 g, 0.025mol) in dry THF (50 mL) at 0 °C was added dropwise a 20 wt % solution of *t*-BuOK in THF (0.0263 mol). The yellow slurry was stirred at room temperature for 45 min, and the hexafluorophosphate salt 29 (8.05 g, 0.0263 mol) was added in one portion. The resulting mixture was stirred at room temperature for 45 min and transferred dropwise with a cannula under nitrogen pressure to a solution of acetic acid (0.175 mol) and TFA (0.02 mol) in THF (25 mL) at 25−30 °C. The mixture was stirred for 45 min, and ammonium hydroxide (15 mL, 0.25) was added in one portion. The resulting dark solution was heated at reflux for 3 h and cooled to ambient. The phases are cut, and the organic layer was concentrated under reduced pressure. Column chromatography on silica gel eluting with ethyl acetate/hexane gave the bipyridine as a colorless solid (8.42 g) in 94% yield. R_f 0.5 IPA/hexane/triethylamine (69:30:1); DSC onset 136.7 °C, peak 138.1 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.69 (d, 1H, J = 2.3 Hz), 8.36 (3, 1H, J = 2.2 Hz), 7.88 (d, 2H, J = 8.4 Hz), 7.72 (d, 1H, J = 2.3 Hz), 7.54 (dd, 1H, J_1=8.0 Hz, J_2=2.3 Hz), 7.38 (d, 2H, J = 8.5 Hz), 7.07 (d, 1H, J = 8.0 Hz), 3.06 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 158.4, 152.2, 149.7, 148.3, 143.7, 140.1, 137.9, 137.2, 135.18. 131.1, 130.0, 130.3, 127.8, 122.7, 44.4, 24.1. Anal. Calcd for $C_{18}H_{15}ClN_2O_2S$. C, 60.25; H, 4.21; N, 7.81. Found: C, 60.30; H, 4.25; N, 7.85.

1-(6-Methyl-3-pyridinyl)-3-(4-methanesulfonylphenyl)-furan 23: mp 203 °C; ^{1}H NMR (400 MHz DMSO-d_6) δ 8.53 (d, 1H, J = 2.4 Hz), 7.90 (m, 2H0, 7.73 (dd, 1H, J_1=8.3 Hz, J_2=2.4 Hz), 7.69 (d, 1H, J = 2.0), 7.62 (m, 2H), 7.23 (d, 1H, J = 8.3 Hz), 6.75 (d, 1H, J = 2.0), 3.08 (s, 3H), 2.52 (s, 3H); (100 MHz $CDCl_3$) δ 158.9, 148.0, 147.1, 144.5, 140.8, 140.1, 135.7, 130.1, 128.7, 125.2, 124.3, 122.8, 114.4, 44.5, 24.0. HRMS Calcd for $C_{17}H_{16}NO_3S$: $[M + H]^+$ = 314.085. Found: 314.087.

2-Chloroaminoacrolein 26. A solution of chloromalonaldehyde (110.5 g, 1.0 mol) in 2-propanol (150 mL) was concentrated to a dark brown oil which was added to a solution of ammonium hydroxide (46 mL) in 2-propanol (200 mL which resulted in an exotherm to 40 °C. The mixture was stirred for 12 h at ambient temperature, and the product was isolated by filtration. The cake was washed with 2-propanol and dried to give the aminoacrolein 26 (84 g) as an off white solid in 80% isolated yield: mp 150−152 °C; ^{1}H NMR (300 MHz $CDCl_3$) L 9.13 (s, 1H), 7.55 (s, 1H); Anal. Calcd C_3H_4ClNO: C, 34.15; H, 3.82; N, 13.27. Found: C, 34.22; H, 3.73; N, 13.11.

2-Chloroaminoacrolein dimer 28: mp 108−109 °C; ^{1}H NMR (200 MHz CD_3CN) δ 9.27 (s, 2H), 7.92 (s, 2H), 2.14 (s, 1H); ^{13}C NMR (100 MHz DMSO-d_6) δ 222.0, 184.4, 156.4. Anal. Calcd for $C_6H_5Cl_2NO_2$: C, 37.14; H, 2.60; N, 7.22. Found: C, 37.15; H, 2.50; N, 7.07.

JO000870Z