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Process Chemistry Related to the Experimental Rice Herbicide 2,2-Dimethyl-1-(4-methylthio-5-pyrimidinyl)indane

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Abstract:

Two concise syntheses of the experimental rice herbicide 2,2-dimethyl-1-(4-methylthio-5-pyrimidinyl)indane are reported. The initial synthesis relies on a low-temperature addition of 5-lithio-4-methylthiopyrimidine to 2,2-dimethyl-1-indanone to construct the pyrimidinylindane system. Process improvements to this route are described and resulted in the preparation of 90 kg of the title compound on pilot plant scale. Economics dictated the need to identify a new synthetic route which utilized inexpensive raw materials. Detailed herein is the initial discovery of a new route which features a novel combination of dissolving metal reduction/formylation/cyclization to construct the requisite pyrimidine ring. Process improvements to this chemistry have allowed us to deliver an appropriately substituted pyrimidinylindane in a minimal number of synthetic operations.

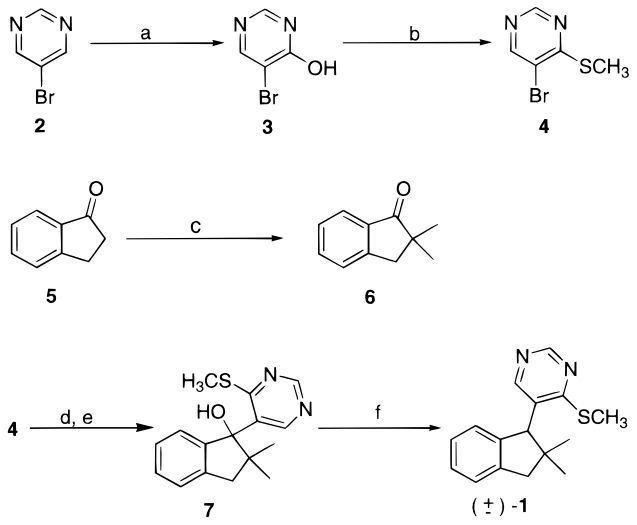
Introduction

In 1994, Markley and co-workers at Dow AgroSciences,[1] discovered a new series of compounds which exhibited herbicidal activity against a variety of weed species in paddy rice. One of the more active and selective members of the series was 2,2-dimethyl-1-(4-methylthio-5-pyrimidinyl)indane (**1**, Scheme 1). To conduct field, toxicology, and formulation studies, kilogram quantities of **1** were required. Herein, we describe: (1) our initial laboratory scale synthesis of **1** which resulted in the preparation of 2.8 kg of material, (2) pilot plant scale-up to produce 90 kg of **1**, and (3) discovery and process development of a new economically and operationally attractive synthetic route to **1**.

Results and Discussion

Initial Laboratory Synthesis of 1 (Scheme 1, Conditions a). At the onset of our studies, expeditious delivery of kilogram quantities of **1** was required to meet a rapid development strategy. Our laboratory synthesis, depicted in Scheme 1 (conditions a), was very similar to that used initially by our Dow AgroSciences colleagues in Discovery Research. Hydroxylation of 5-bromopyrimidine via a literature procedure[2] provided pyrimidone **3** which was chlorinated and then substituted with thiomethoxide, providing the 4,5-disubstituted pyrimidine **4**. Indanone **6** was prepared by geminal dialkylation of 1-indanone (**5**). Metal halogen exchange of **4** at −85 °C, followed by introduction of electrophile **6** yielded tertiary alcohol **7**. Lewis acid mediated silane reduction[3] furnished the desired product **1**. Preliminary investigation of this chemistry in our laboratories identified two major scale-up issues. The first is a reactive chemicals issue for the literature peracid hydroxylation of 5-bromopyrimidine (**2**).[2] We found that a significant amount of the explosive acetone peroxide is formed when acetone is used as the solvent.[4] Thus, a totally aqueous hydroxylation system was developed which provided comparable yields to that reported in the literature. The second scale-up issue was the moderate yield (∼55%) of the low-temperature organometallic step, which complicated purification of alcohol **7**. Upon manipulation of several reaction parameters, improved results were obtained when a THF solution of **4** was added dropwise to *n*-butyllithium/hexane/THF below −85 °C. Following introduction of ketone **6**, workup and digestion with ethanol, the product, **7**, was obtained in 74% yield (98+% pure). For the conversion of **5** to **6**, we found that powdered potassium hydroxide in DMSO could be used for the alkylation.

Scheme 1 [a,b]



[a] Conditions: (a) H_2SO_4, peracetic acid, acetone; (b) $SOCl_2$, cat. DMF then $NaSCH_3$, CH_3CN, IPA; (c) powdered KOH, CH_3I, DMSO: (d) nBuLi, THF, hexanes; (e) **6**, THF; (f) BF_3•OEt_2, CH_2Cl_2, Et_3SiH. [b] Conditions: (a) H_2SO_4, peracetic acid, water; (b) $SOCl_2$, cat. DMF, toluene chase; thiourea, ethanol; KOH, water; $(CH_3)_2SO_4$; (c) KOH, CH_3I, NMP, water; (d) nBuLi, toluene, hexanes; (e) **6**, toluene; (f) CF_3CO_2H, $NaBH_4$, CH_2Cl_2.

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(1) Markley, L. D.; Arndt, K. E.; Ray, P. G.; Balko, T. W.; Cressman, E. N. K.; Ouse, D. G.; Jackson, J. L.; Secor, J. 4-Substituted 5-polycyclylpyrimidine herbicides. U.S. Patent 5,780,465, 1998, 36 pp. CODEN: USXXAM US 5780465 A 19980714 CAN 129:105503.

(2) Kress, T. J. *J. Org. Chem.* **1985**, *50*, 3073.

(3) Adlington, M. G.; Orfanopoulos, M.; Fry, J. F. *Tetrahedron Lett.* **1976**, 2955.

(4) Dietsche, T. J.; Powers, B. Explosion in preparation of 5-bromo-4(3H)-pyrimidinone. *Chem. Eng. News* **1995**, *73*, 4 (July 10, 1995).

10.1021/op000033z CCC: $19.00
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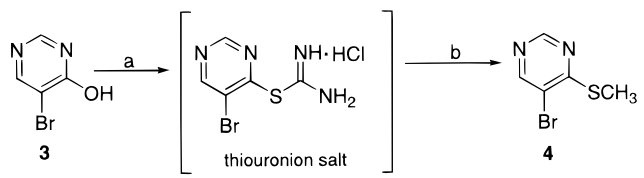
Precipitation of the product by addition of water led to simple isolation of pure **6**. The preparation of **1** using these modifications is detailed in the Experimental Section.

Process Improvements and Pilot Plant Scale-Up (Scheme 1, Conditions b). Although the synthetic route described above can be used to conveniently prepare kilogram quantities of **1** in the laboratory, several of the steps are not amenable to scale-up in a pilot plant facility. Improvements that address these issues will now be described. The peracid oxidation of **2** was found to go to completion much faster at 70−75 °C with no affect on yield or product quality. The resulting pyrimidone (**3**) was isolated by centrifugation and then suspended in toluene. Azeotropic removal of the water followed by centrifugation provided a toluene wet cake of **3** which was used directly in the subsequent chlorination. This oxidation was conducted in three batches utilizing a 300 gallon reactor and resulted in an overall yield of 197 kg (65%) of **3**.

The previous method for the conversion of **3** to **4** is outlined in Scheme 1 (conditions a). Chlorination of **3** using thionyl chloride as solvent (DMF catalysis) followed by removal of the excess thionyl chloride via distillation provided the crude 5-bromo-4-chloropyrimidine as a brown oil. Treatment with sodium or potassium thiomethoxide in 2-propanol/acetonitrile followed by dilution of the reaction mixture with water afforded an aqueous slurry of the desired product. Filtration, followed by drying the material to a constant weight, provided 80−85% yields of methylthiopyrimidine **4**. The chemistry described works well, but this process has two major drawbacks when considering pilot plant operations. The first is the need to dry large quantities of **4** as a solid, and the second is the odor problem associated with the use of thiomethoxide. The first problem was easily circumvented by extractive removal (toluene) of **4** from an aqueous mixture, followed by azeotropic drying of the extract. A solution to the odor problem presented itself when a literature search revealed an alternate preparation of **4** using odorless thiourea as the source of sulfur.[5] Utilizing this chemistry, we devised a two-pot method for the thiomethylation of **3**. The chlorination reaction was run as previously described. After distillation of the bulk of the thionyl chloride, residual thionyl chloride was removed using a toluene chase. The resulting toluene solution of the chloropyrimidine was added to thiourea in ethanol, causing rapid displacement of the heterocyclic chloride, yielding the

Scheme 2 [a]



[a] Conditions: (a) $SOCl_2$, cat. DMF; toluene chase; thiourea, ethanol; (b) KOH, water then $(CH_3)SO_4$.

corresponding thiouronium salt (Scheme 2). Addition of aqueous potassium hydroxide effected hydrolysis, and the resulting potassium thiolate was S-alkylated with dimethylsulfate. Work up of the reaction consisted of dilution with water and extraction with toluene. The organic phase was washed with brine, water and then dried azeotropically to provide a toluene solution of **4** (15−28 wt. % via HPLC analysis). Yields for this procedure were 75−85% based on the initial charge of 5-bromo-4-hydroxypyrimidine (**3**). One major impurity (2−3 area % by GC) is produced and has been identified as an isomer of **4** (GC/MS). The most likely structure of this impurity is the alkylation regioisomer, *N*-methylthione. This chemistry was conducted in three batches, utilizing two 300 gallon reaction vessels and provided 165 kg (81%, 97+% purity) of **4**.

The process to prepare the 2,2-dimethyl-1-indanone (**6**) for the 2.8 kg campaign involved the use of DMSO, powdered KOH, and methyl iodide. For scale-up to a pilot plant, both powdered KOH and DMSO create potential problems. Although the reaction is carried out below room temperature, the possibility for the known decomposition of DMSO at higher temperatures is always present due to the exothermic nature of the alkylation chemistry. Indeed, an adiabatic temperature rise of about 140 °C is possible, based on a calculated heat of reaction of −65 to −77 kcal/mol for the formation of 2,2-dimethyl-1-indanone (**6**). Powdered KOH, although easy to prepare in the laboratory from pellets using a blender, would be difficult and time-consuming in the plant. With a minimal amount of time and research, solutions were found for both concerns (Scheme 1, conditions b). First, *N*-methylpyrrolidinone proved to be an excellent choice for a solvent. The reaction yields were the same as for DMSO. Second, the use of 45% aqueous KOH turned out to be better than the use of the powdered form from a standpoint of ease of addition. Instead of adding solid powdered KOH into a mixture of the indanone **5** and methyl iodide in the solvent, the 45% solution could be added dropwise. One difficulty encountered with 45% KOH was that there were two phases in the pot until 35−50% of the base was added. When complete solution was achieved, an exotherm ensued, taking the batch from 20 to 60−70 °C, indicating a rapid reaction. By changing the order of addition (adding the NMP solution to the KOH), the reaction started immediately, and the exotherm could easily be controlled. Finally, the reaction outcome seemed to be insensitive to variation in temperature. Whether the pot temperature was kept below 20 °C or allowed to warm to 60−70 °C, yields and purity did not change significantly. A temperature of 25 °C was chosen for the pilot plant conditions. The alkylation of 1-indanone (**5**) was conducted in seven batches, utilizing a 100 gallon reactor, thus yielding a total of 119 kg (81%, 97+% pure) of **6**.

The metal halogen exchange of **4** and nucleophilic addition to ketone **6** was carried out as previously described with two process modifications (Scheme 1, conditions b). First, to improve process flow, the previously dried toluene solution of heteroarylbromide **4** (15−28%) was added to the *n*-butyllithium\THF\hexane mixture at −85 °C, thus affecting metal halogen exchange. After additon of ketone **6** and warming the mixture to −20 °C, the reaction was quenched

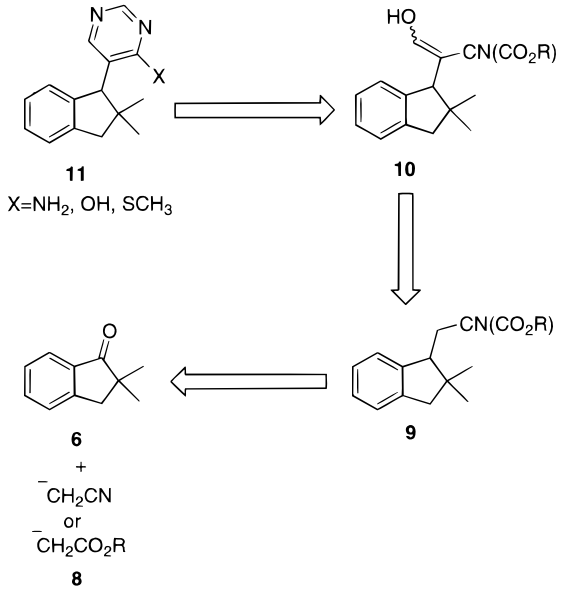
(5) Brown, D. J.; Foster, R. V. *Aust. J. Chem*. **1966**, *19*, 2321−30.

with water. Most of the hexane and THF were removed via simple distillation, followed by dilution of the heterogeneous mixture with water. The toluene was removed by azeotropic distillation with water and the resulting warm aqueous slurry was diluted with an equal volume of ethanol. After cooling to ambient temperature, the solid product (**7**) was collected by filtration, washed with water, and dried. Utilizing this modified procedure, laboratory yields of 73−82% were obtained on a one mole scale (five-liter equipment). Five batches were scaled to a 200 gallon cryogenic reactor and resulted in production of 107 kg (57% yield, 99+% purity) of tertiary alcohol **7**.

In our previous synthesis, we described the conversion of tertiary alcohol **7** to **1** using boron trifluoride etherate and triethysilane as the reducing medium. Although these conditions afforded good yield (~80%) and were practical on laboratory scale, the price of triethylsilane made scale-up cost prohibitive. Thus, we developed a new lower-cost procedure which involves addition of trifluoroacetic acid to a 0.5 M solution containing **7** in methylene chloride with suspended sodium borohydride pellets[6] which gave clean conversion to **1** at about 0 °C (Scheme 1, conditions b). After an aqueous extraction, followed by an aqueous extraction/neutralization using sodium hydroxide, the organic layer was concentrated, and methylene chloride was exchanged with methanol. Following crystallization from methanol, water was added to the slurry to complete the crystallization. The product was collected by filtration, washed with water, and dried. On the basis of a product assay of 98.1%, a 94% yield of **1** was obtained on a 0.46 mol scale. Scale-up to a 100 gallon reactor afforded 91 kg (88%, 99+% purity) of **1** in three runs.

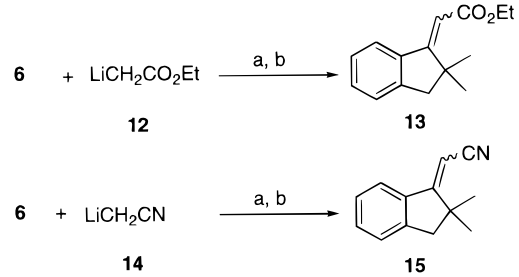
Discovery of a New Synthetic Route to 1. During the course of our initial sample campaigns, it became evident that we could not meet the required long-term cost of manufacture utilizing the chemistry described above. It became clear to us that a cost-effective synthesis of **1** must rely on construction of the requisite 4,5-disubstituted pyrimidine from inexpensive raw materials in a minimal number of unit operations. Since 2,2-dimethyl-1-indanone (**6**) had the potential of supplying the indane backbone of **1** at reasonable cost,[7] our initial studies focused on this as the key starting material. Our strategy, depicted in Scheme 3, was to use the carbonyl of **6** as an electrophile in combination with a heteroatom-stabilized carbanion (**8**) to construct the carbon−carbon bond at what would eventually be the 5-position of the pyrimidine. After reduction, it was our intent to obtain **9**, which under strongly basic conditions may be induced to undergo formylation to afford an intermediate such as **10**. β-Aldehydo nitriles such as **10** are well-known precursors of 4-functionalized-5-substituted pyrimidines[8] represented by the general structure **11**. Incorporation of a methylthio substituent at the 4-position of the pyrimidine would provide our target, **1**.

Scheme 3



Our initial laboratory investigations focused on identification of carbon nucleophiles that would efficiently undergo addition to the carbonyl of **6**. It was anticipated that steric hindrance in conjunction with conjugation of the carbonyl[9] would cause **6** to be reactive with only the most efficient nucleophiles. This indeed proved to be the case. Attempted reaction of **6** with Meldrum's acid, diethyl malonate, or malononitrile under standard or modified Knoevenagel conditions[10] led to extremely low yields (<10%) of impure products. However, reaction of **6** with strong (e.g., conjugate acid pK_a's of ~25), sterically nondemanding carbanions afforded the desired addition products, which underwent dehydration upon treatment with acid (Scheme 4). For

Scheme 4 [a]



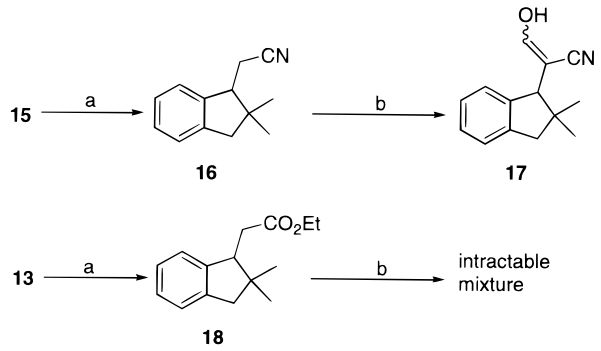
[a] Conditions: (a) THF, Hexane, −70 °C; (b) *p*-TsOH, toluene, $-H_2O$.

example, generation of lithioethylacetate (**12**) followed by treatment with **6** and subsequent dehydration provided a mixture of olefin isomers **13** in 79% yield following distillation. Likewise, reaction of lithioacetonitrile (**14**) with **6** followed by dehydration gave the desired olefins **15** in 83% yield.

With ample supplies of **13** and **15** available, studies were initiated to investigate the feasibility of pyrimidine ring construction. Catalytic hydrogenation of the double bonds

(6) Gribble G. W.; Leese, R. M.; Evans, B. E. *Synthesis* **1977**, 172.
(7) Bruson, H. A.; Plant, J. L. *J. Org. Chem*. **1967**, *32*, 3356.
(8) For a general review of the synthesis of pyrimidines from dicarbonyls and equivalents see: Brown, D. J. *Heterocyclic Compounds; The Pyrimidines*; Wiley & Sons: New York, 1994; Chapters 2 and 3.
(9) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley & Sons: New York, 1992; ;Chapter 16, p 881.
(10) For a review of the Knoevenagel reaction see: Jones, G. *Organic Reactions*; Wiley & Sons: New York, 1967; Vol. 15, p 204.

Scheme 5 [a]

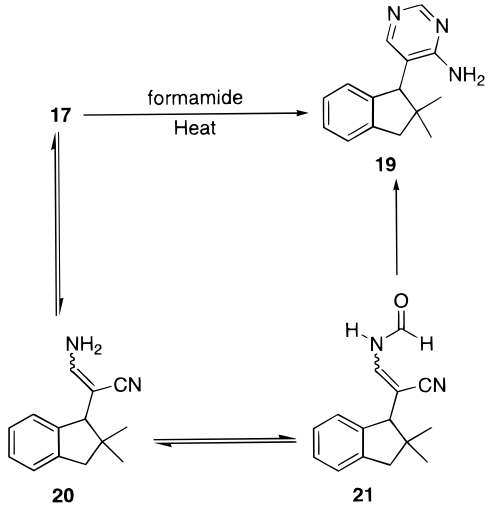


[a] Conditions: (a) H_2, Pd/C, EtOH; (b) LDA, THF, −70 °C then ethyl formate.

of **13** and **15** provided the nitrile **16** and ester **18** in excellent yield (95−100%, Scheme 5). Generation of the nitrile α-anion of **16** with lithium diisopropylamide (LDA) followed by treatment with ethyl formate afforded the aldehydo-nitrile **17** in good yield (76%). However, much to our surprise, exposure of ester **18** to the same reaction conditions did not afford the anticipated product but yielded an intractable mixture of unidentified products. This reaction was attempted several times, producing, in all cases, similar results. Because **17** had been obtained in good yield, no further time was invested to understand this unexpected decomposition.

Treatment of β-dicarbonyl or equivalent compounds (i.e., β-aldehydo-nitriles such as **17**) with formamide at 150−200 °C can provide 5-alkyl pyrimidines.[8] This reaction, known as the Bredereck pyrimidine synthesis, has fairly wide applicability but generally delivers the products in low to moderate yield. We have found that exposure of **17** to the Bredereck conditions affords the amino pyrimidine **19** in good yield (72%) following removal of tars via filtration through silica gel. The reaction pathway from **17** to **19** has been elucidated with the aid of gas chromatography/mass spectrometry (GC/MS) analyses performed during the course of the reaction and by synthesis and characterization of the intermediates **20** and **21** (Scheme 6).[11] Initial warming of

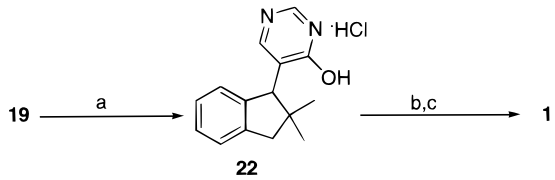
Scheme 6



17 in the presence of formamide leads, rather quickly, to formation of the enamino-nitrile isomers **20** which on continued heating undergo N-formylation to **21**. Further heating leads to ammonia incorporation followed by irreversible intramolecular cyclization providing amino pyrimidine **19**. The cyclization is generally complete in about 3 h at 185 °C. Prolonged heating can cause N-formylation of the amine substituent of **19**. The slow decomposition of formamide to carbon monoxide and ammonia provides the requisite ammonia source.

At this juncture it had been shown that the desired 4,5-disubstituted pyrimidine could be formed in a straightforward manner from readily available materials. What was left to demonstrate, was the conversion of the amine group of **19** to the methylthio substituent contained within **1**. Towards this end, the one-pot anhydrous diazotization/disulfide trapping reaction of aromatic amines was attempted.[12] Treatment of a solution of **19** with *tert*-butyl nitrite and dimethyl disulfide in a variety of solvents resulted in formation of a dark reaction mixture in which no **1** could be detected via GC/MS analysis.

Scheme 7 [a]



[a] Conditions: (a) HCl, H_2O, heat; (b) $SOCl_2$, cat. DMF; (c) $NaSCH_3$, CH_3OH.

Scheme 7 presents an efficient albeit less direct route from **19** to **1**. Hydrolysis of **19** to the corresponding hyroxypyrimidine hydrochloride **22**[13] was accomplished in refluxing aqueous hydrochloric acid. Conversion of **22** to the corresponding chloropyrimidine was effected under standard conditions. Substitution of thiomethyl for chloro provided **1** which was identical to material prepared by the previous synthetic route.

Having proven that the strategy depicted in Scheme 3 is viable, we undertook several short investigations, with the aim of decreasing the number of synthetic steps and the cost of certain reagents. For the conversion of indanone **6** to unsaturated nitrile **15** (Scheme 4), LDA was used to generate the nitrile anion.[14] Since LDA is prepared by the action of *n*-butyllithium on diisoproplyamine, the use of such a base on commercial scale would be cost-prohibitive. Gokel and co-workers[15] have described generation of the acetonitrile anion using powdered potassium hydroxide in acetonitrile

(11) Enamino-nitrile **20** can be independently synthesized by the reaction of **17** with ammonia in an appropriate solvent. The formylated material **21** has been prepared via the reaction of **20** with acetic-formic mixed anhydride in toluene. See the Experimental Section. Exposure of both of these materials to the Bredreck conditions afforded pyrimidine **19**.

(12) Beck, J. R.; Ackmann, S. A.; Staszak, M. A.; Wright, F. L. *J. Heterocycl. Chem*. **1988**, *25*, 955.

(13) We have represented the structure of **22** to be a hydrochloride salt. However, we cannot rule out that the actual structure may be a covalent HCl addition product.

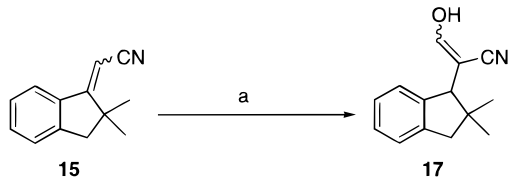
(14) For a general review of the generation and use of nitrile anions see: Arseniyadis S.; Kyler, K. S.; Watt, D. S. *Organic Reactions*; Wiley & Sons: New York, 1984; Vol. 31, p 1.

(15) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem*. **1979**, *44*, 4640.

as solvent and subsequent addition to carbonyl compounds. We were skeptical about the application of this methodology to ketone **6** due to its unreactive nature and the possibility of generating acetonitrile oligimers. Nonetheless, the potential long-term economic savings enticed us to conduct a brief laboratory investigation of the method. Although this method did deliver **15** in about 50% distilled yield, a significant quantity of intractable tars (acetonitrile oligimers) remained behind following distillation. Attempts at phase-transfer catalysis and several other variants did not improve matters. Alkoxide bases also provided dismal results for this reaction. It appears as if complete deprotonation of acetonitrile with an appropriate strong base is necessary for an efficient condensation with **6**.

Another synthetic step which was bothersome to us due to the use of the expensive base LDA, was the conversion of nitrile **16** to enol-nitrile **17** as shown in Scheme 5. Upon more in-depth analysis of the conversion of unsaturated nitrile **15** to the desired enol-nitrile **17**, we reasoned that if **15** could be induced to undergo a 1,4-type hydride reduction under aprotic conditions the desired α-nitrile anion would be generated. Introduction of the formate electrophile at this point could provide a one-pot conversion of **15** to **17** and also eliminate the need for the strong base LDA. Not long after the formulation of this idea, we came to the realization that a dissolving metal reduction may provide a simple, inexpensive solution to the problem. Indeed, treatment of an ammonia/THF solution (−50 to −60 °C) of **15** with about two equivalents of sodium metal in the presence of one equivalent of *tert*-butyl alcohol resulted in an initial blood red color. As the final pieces of metal dissolved, the color changed to deep blue, indicating that the reduction phase was complete. Addition of ethyl formate followed by warming to room temperature and workup provided **17** in 80% yield on the first attempt (Scheme 8). During the course

Scheme 8 [a]

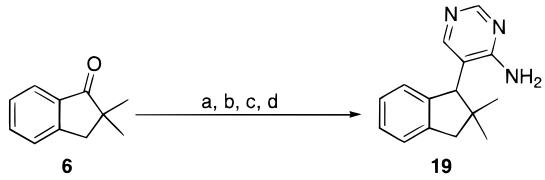


[a] Conditions: (a) Na, NH_3, THF then ethylformate.

of conducting subsequent reactions we found this method to be fairly robust. For example, the reaction can be run near the boiling point of ammonia (−33 °C), and the THF may be replaced with the less expensive solvent toluene. The sodium metal may be added to a solution of **15** in toluene/ammonia, or a toluene solution of **15** may be added to sodium dissolved in ammonia. The addition of one equivalent of *tert*-butyl alcohol as the proton source is not necessary, thus indicating that a very strong base, capable of abstracting a proton from the ammonia solvent, is formed during the course of electron transfer.[16] Whether this extremely basic intermediate is a dianion or radical-anion is not known; however, we do assume that this intermediate is responsible for the blood-red color. If a process utilizing sodium and liquid ammonia is to be implemented, this brings about the possibility of preparing the strong base sodium amide for use in other steps of the synthesis. A 1968 report by Kaiser and Hauser[17] describe the high-yielding generation of the acetonitrile anion using sodium amide in liquid ammonia and its subsequent addition to carbonyl compounds. Application of this technology toward a high-yielding conversion of **6** to **15** and thus eliminating the need for the expensive base LDA is described in the following section. At this juncture, a new synthetic route to **1** had been demonstrated on laboratory scale. The route, which begins with 2,2-dimethyl-1-indanone (**6**), utilizes inexpensive raw materials and features a novel combination of dissolving metal reduction/formylation/cyclization to deliver a complex amino pyrimidine intermediate in a reasonable number of synthetic operations. This pyrimidine intermediate has been converted to **1** under standard reaction conditions.

Development of the New Route. Having demonstrated that a new, more economical synthetic route to **1** was viable, our team turned its attention to development of a reliable, efficient process involving a minimal number of unit operations. As a result of significant laboratory study, we have found that ketone **6** can be converted to aminopyrimidine **19** in two reaction vessels and requires only three simple workup procedures. Thus, a suspension of sodium amide is prepared in liquid ammonia and then treated with anhydrous acetonitrile in toluene to produce the nitrile anion (Scheme 9). Introduction of ketone **6** in toluene effects 1,2-addition,

Scheme 9 [a]



[a] Conditions: (a) Na, NH_3, cat. $Fe(NO_3)_3 \cdot 9H_2O$; CH_3CN, toluene; (b) H_2SO_4, toluene; (c) Na, NH_3, toluene, methyl formate; (d) formamide, heat.

and the resulting alkoxide is then quenched into cold aqueous hydrochloric acid. It is worth noting that addition of the aqueous acid to the alkoxide causes significant reversal of the addition reaction.[17,18] The phases are separated, and the organics freed of hydrochloric acid and chloride salts by washing with water.[19] Azeotropic drying of the toluene solution in the presence of a catalytic amount of sulfuric acid affords a toluene solution of the nitrile isomers **15**. This solution is added to sodium metal dissolved in liquid ammonia to effect dissolving metal reduction/anion generation. The mixture is quenched with methyl formate followed by an anhydrous proton source (ammonium chloride). Distillation of the ammonia is performed with concomitant

(16) For a review of metal/ammonia reductions of α-*β* unsaturated compounds see: Caine, D. *Organic Reactions*; Wiley & Sons: New York, 1976; Vol. 23, p 1.

(17) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.

(18) Beam, C. F. *Can. J. Chem.* **1978**, *56*, 2572.

(19) Failure to remove chloride salts from the organic layer dictated the use of increased amounts of sulfuric acid to complete the subsequent dehydration, due to the formation and evaporative loss of hydrogen chloride.

addition of formamide. Heating the mixture to 185 °C for 3 h completes the pyrimidine cyclization. Upon cooling and adding water/toluene, the desired aminopyrimidine (**19**) was isolated as an off-white solid by simple filtration. The addition of toluene during the work up is an inexpensive method of removing tars, which had been previously separated by chromatography. Our process provides consistent yields (60−65% from **6**) of high purity material (98+ wt %). This high-yielding sequence of reactions is remarkable when one considers the number of chemical bonds being formed and broken while utilizing a minimal number of physical operations! The pyrimidine amine **19** was then converted to **1** in three steps as depicted in Scheme 7.

Conclusions

In summary, we have reported two synthetic routes to the experimental herbicide **1**. Although our initial route has only six synthetic steps and was amenable to pilot plant scale-up, it relies on expensive raw material and reagents. Economic evaluation of this route has shown it to be incapable of producing **1** at a viable cost/kg. These economic considerations dictated our discovery of a new route to **1** which begins with 2,2-dimethyl-1-indanone and utilizes inexpensive raw materials and reagents. This new route involves carbon−carbon bond formation reactions of two nitrile-stabilized carbanions which are generated from the inexpensive reagents sodium and liquid ammonia. A one-pot dissolving metal reduction/formylation/Bredreck cyclization is employed and delivers a complex amino pyrimidine intermediate in a minimal number of unit operations. This pyrimidine intermediate is converted to **1** using standard methods.

Experimental Section

Reagents and solvents were reagent and technical grade and used as received. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solvents were evaporated in vacuo using a Buchi rotary-evaporator. The ^{1}H NMR and ^{13}C NMR spectra were determined using a Bruker AC-300 instrument in the solvent noted. Mass spectra were determined using a Hewlett-Packard GCD system operating at 70 eV in the electron impact mode. Gas chromatography (GC) was performed using a Hewlett-Packard 5890A instrument containing Restek Rtx-5 column (15 m × 0.32 mm, 0.25 um film) under the following conditions: temp1 = 100 °C, time1 = 1 min, rate = 20 °C/min, temp2 = 275 °C, time2 = 10 min, 5 psi helium head pressure, FID detection or temp1 = 60 °C, time1 = 1 min, rate = 20 °C/min, temp2 = 275 °C, time2 = 10 min. High performance liquid chromatography (HPLC) was conducted on a Keystone Scientific Phenylhypersil-1 column (250 × 4.6 mm, 5um) using mixtures of acetonitrile\water (0.05% H_3PO_4) as the eluent. Detection was, in general, by UV at 214 nm. Thin-layer chromatography (TLC) was routinely used to monitor reactions. TLC was conducted on precoated Analtech silica GF/UV_{254} plates (250 um layer). Column chromatography was conducted using silica gel 60 (230−400 mesh, Selecto Scientific). Elemental analyses were carried out by Galbraith laboratories, Knoxville, TN.

5-Bromo-4-hydroxypyrimidine (3). A 5-L three-neck round-bottom flask was equipped with a mechanical stirrer, a thermowell, and a 500 mL addition funnel. To the reactor was charged water (1500.0 g) followed by slow addition of H_2SO_4 (255.0 g, 2.6 mol) via the addition funnel. The warm solution was cooled (ice bath) to ∼20 °C. To the reactor was then added 5-bromopyrimidine (410.0 g, 2.58 mol). To the slurry was then slowly added, via the addition funnel, 32% peracetic acid (628.0 g, 2.64 mol) at a rate where the pot temperature did not exceed 70 °C with cooling (ice bath). The slurry turned to a solution after two-thirds of the peracetic acid was added. The reaction was stirred at 70 °C for 2 h at which time analysis of the reaction solution by gas chromatography indicated >99% product by area %. The reaction was cooled to ∼50 °C, and to it was slowly added a solution of Na_2SO_3 (110.0 g, 0.87 mol) in 500.0 g of water. The pot temperature was maintained at <70 °C with an ice bath. Starch iodide test of the reaction solution was negative after the addition was completed. The reaction was cooled to ∼50 °C, and to it was slowly added 50 wt % NaOH (580.0 g, 7.25 mol) solution while a pot temperature of <70 °C was maintained with an ice bath. The slurry of off-white precipitate was cooled to 20 °C. The solids were collected in a Buchner funnel, and the off-white wet cake was rinsed with water (2 × 500.0 g). The wet cake was transferred to a 1-L three-neck round-bottom flask equipped with a mechanical stirrer, a thermowell, and Dean−Stark trap with a cold-water condenser. To the reactor was added 750 mL of toluene. The toluene slurry was heated to reflux, and the mixture was azeotropically dried, after which approximately 250 mL of toluene was removed by distillation. The reaction mixture was cooled to ambient temperature, and the crystals were collected by filtration as a toluene wet cake (415 g of 11% toluene wt cake, 83%). The melting point of a dried sample was 198−203 °C; ^{13}C NMR (DMSO-d_6) 113.3, 149.6, 154.1, 157.6; recrystallization from water provided an analytical sample; Anal. Calcd for $C_4H_3BrN_2O$: C, 27.46; H, 1.73; N, 16.01. Found: C, 27.41; H, 1.71; N, 16.00.

5-Bromo-4-methylthiopyrimidine (4). A 1-L three-neck round-bottom flask with thermowell was fitted with a mechanical stirrer, condenser/$CaSO_4$ drying tube and a stopper. The vessel was loaded with a toluene wet cake of **5** (291 g of ∼83 wt. %, ∼1.35 mol) and thionyl chloride (570 g, 4.8 mol). The slurry was treated with DMF (4.0 mL, 0.052 mol), and the mixture was heated to reflux and held there for 2.5 h, at which time most of the solids had gone into solution. The mixture was allowed to cool slightly, and the condenser was replaced with a short-path distillation apparatus. Thionyl chloride was distilled (condenser temperature at 50 °C) to a final pot temperature of 132 °C, resulting in 327 g of yellow distillate which contained a small amount of solid. The internal temperature was cooled to 100 °C, and then toluene (354 g) was added. The distillation was resumed until a pot temperature of 142 °C (111 °C head temperature) was reached, resulting in 335 g of pale yellow distillate. The distillation residue was allowed to cool to 50 °C, resulting in a thin slurry. The warm slurry was added in one portion to thiourea (110 g, 1.45 mol) in ethanol (970 g)

contained in a 5-L three neck round-bottom flask with mechanical stirring and a nitrogen pad. The distillation pot residue was rinsed with toluene (125 g) and this also added to the thiourea slurry. The resulting mixture exothermed to 44 °C over 10 min. After the mixture stirred at ambient temperature for 2 h, the internal temperature had reached 24 °C, and the reaction was judged to be complete via HPLC analysis. The cream-colored slurry was cooled to 15 °C, and then 45% KOH (390 g, 3.13 mol) was added in one portion, causing the internal temperature to rise to 30 °C. The slurry was stirred at ambient temperature for 1.6 h at which time HPLC analysis indicated the hydrolysis was complete. The slurry was cooled to 10 °C, and then dimethylsulfate (165 g, 1.31 mol) was added in a rapid stream over 4 min. The temperature exothermed to 34 °C over 10 min. After the mixture stirred in the cooling bath for an additional 30 min, the internal temperature was 25 °C, and the reaction was judged to be complete as determined by HPLC. The resulting slurry was allowed to stir at room temperature for 1 h, and then water (800 g) and toluene (1200 g) were added. The mixture was vigorously agitated for 10 min and then the phases were allowed to separate. The organic phase was washed with 10% NaCl (400 g) and water (400 g). Drying by azeotropic removal of distillate (365 g) provided a light amber solution of the product (1207 g). Analysis of the toluene solution via GC indicated a purity of 93 area % (t_R = 3.45 min) with the major impurity (2.5%, t_R = 5.77 min) being an isomer of **4**. Reverse phase HPLC analysis of the toluene solution utilizing an external standard method indicated the solution was 17.7 wt % **4** (214 g, ~77% yield). Concentration of a small aliquot provided off-white cystals; mp 73−74 °C; ^{1}H NMR ($CDCl_3$) 2.56 (s, 3H), 8.44 (s,1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$) 13.4, 118.7, 155.0, 155.7, 169.7; MS (GC) 206, 204 (M^+, 25, 25), 125 (100), 52 (50); Anal. Calcd for $C_5H_5BrN_2S$: C, 29.28; H, 2.46; N, 13.66. Found: C, 29.39; H, 2.56; N, 13.69.

2,2-Dimethyl-1-indanone (6). A 5-L four-neck round-bottom flask was fitted with condenser, mechanical stirrer, thermowell, and addition funnel. To this was added 623 g of 45% KOH, and the solution was cooled to below 10 °C. To 1 L of NMP was added 264.4 g (2 mol) of 1-indanone (**5**) and 600 g (4.22 mol) of methyl iodide with stirring until the indanone dissolved. The indanone solution was added dropwise over 1.5 to 2 h to the KOH. The temperature varied between 8 and 29 °C and was controlled by an ice bath and by adjusting the rate of addition. After the addition was complete, the mixture was stirred for 1.5 h, and GC area % analysis showed 96% **6**. The mixture was cooled to below 10 °C, 2.5 L of water was added, and the solid product was stirred for an additional 0.5 h. The off-white crystals were filtered, washed twice with 1 L of water, and air-dried for 40 h to yield 284 g of **6** (89%); mp 40−42 °C; ^{1}H NMR ($CDCl_3$) 1.20 (s, 6H), 2.97 (s, 2H), 7.34 (m, 2H), 7.55 (apparent t, 1H), 7.72 (d, 1H); MS (GC) 160 (M^+, 40), 145 (100).

2,2-Dimethyl-1-(4-methylthio-5-pyrimidinyl)indan-1-ol (7). A nitrogen-purged 5-L three-neck round-bottom flask with thermowell was fitted with a mechanical stirrer and a graduated addition funnel with septum and nitrogen inlet. To the flask was added *n*-BuLi (388 mL of 2.5 M in hexanes, 0.97 mol) via cannula. The solution was cooled to ~−50 °C (dry ice/ethanol bath), and anhydrous THF (1455 mL) was added. The solution was cooled to ~−85 °C (liquid nitrogen/ethanol bath) and a 15 wt % solution of 5-bromo-4-methylthiopyrimidine (1332 g, 0.97 mol) in toluene was added dropwise at a rate such that the internal temperature did not exceed −80 °C. The resulting solution was stirred for 1 h at −95 to −90 °C. A solution of 2,2-dimethylindan-1-one (**6**, 155.2 g, 0.97 mol) in THF (340 mL) was added at a rate such that the internal temperature remained below −80 °C. The cooling bath was removed and the dark brown solution allowed to warm slowly to −25 °C and quenched with water (250 mL). The vessel was fitted with a 30 cm Vigreux column, and volatiles were removed at atmospheric pressure (pot temperature 66−110 °C, head temperature 55−97 °C). After the dark mixture was allowed to cool to 90 °C, water (1500 mL) was added and distillation continued. The internal temperature was slowly raised to 101 °C (head temperataure 93 °C) and a colorless distillate collected (788 g, ~880 mL). The dark orange slurry was cooled to 80 °C, and ethanol (1500 mL, 200 proof) was added. After the slurry cooled to ambient temperature with good stirring, the precipitate was collected via vacuum filtration. The orange solids were slurry-washed with water (500 mL) and pulled as dry as practicable on the filter. The resulting wet cake (243 g) was air-dried to a constant weight, affording the product as a tan solid (206 g, 74% yield). Reverse phase HPLC analysis and GC analysis both indicated that the material was 99+ area % pure; mp 184−186 °C; ^{1}H NMR ($CDCl_3$) 0.93 (s, 3H), 1.31 (s,3H), 2.53 (s, 3H), 2.58 (s, 1H), 2.80 (ABq, J = 15.8, 66 Hz, 2H), 7.25 (m, 4H), 7.52 (s, 1H), 8,80 (s, 1H); MS (GC) 286 (M^+, 45), 271 (30), 253 (20), 239 (100), 183 (60), 115 (55); Anal. Calcd for $C_{16}H_{18}N_2OS$: C, 67.10; H, 6.34; N, 9.78. Found: C, 67.13; H, 6.52; N, 9.73.

2,2-Dimethyl-1-(4-methylthio-5-pyrimidinyl)indane (1). To a 3-L round-bottom flask equipped with an overhead stirrer, addition funnel, thermometer, and nitrogen inlet were added 131.7 (0.46 mol) of **7**, 9.7 g (0.26 mol, 0.56 mol equiv) of sodium borohydride pellets (11 mm diameter), and 900 mL of methylene chloride. The mixture was cooled to −3 °C, and 699.9 g (6.13 mol, 13.3 mol equiv) of trifluoroacetic acid was added over 0.5 h, maintaining the temperature below 2 °C. After stirring between 0 and −2 °C for 3 h, the mixture was gradually warmed to room temperature and allowed to stir overnight (total reaction time 24 h). After the mixture was cooled to 5 °C, the clear, amber/orange solution was extracted with 500 mL of water. After 200 mL of water was added, the mixture pH was adjusted from <1 to >12.5 by adding 443.6 g of 5 N aqueous sodium hydroxide over 6 min, using an ice bath to keep the temperature ≤26 °C. After the layers were separated, the organic layer was concentrated to 209 g on a rotary evaporator. After 399.8 g of methanol was added, the mixture was concentrated to 353.6 g. The slurry was diluted with 251.5 g of water and was stirred for 30 min at room

temperature. The slurry was filtered, and the solids were washed with 100 mL of water. The product was dried at about 65 °C on a rotary evaporator, giving amber, sugar-like solids. A total of 119.0 g of solids were obtained which assayed at 98.1% by HPLC, giving a calculated yield of 116.8 g (94%). Recrystallization from methanol/water provided an analytical sample; mp 94−95 °C; ^{1}H NMR ($CDCl_3$) 0.88 (s, 3H), 1.32 (s, 3H), 2.60 (s, 3H), 2.85 (Abq, J = 15.7, 20.4 Hz, 2H), 4.32 (s, 1H), 6.93 (d, J = 7.3 Hz, 1H), 7.12−7.27 (m, 3H), 7.71 (s, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$) 12.9, 24.2, 30.2, 45.7, 47.2, 55.0, 124.8, 125.0, 126.8, 127.3, 132.8, 143.2, 144.2, 154.1, 155.9, 169.8; MS (GC) 270 (M^+, 55), 255 (100); Anal. Calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; H, 10.36. Found: C, 71.18; H, 6.71; N, 10.23.

***E*- and *Z*-2-(2,2-Dimethyl-1-indanylidene)acetonitrile (15).** To a cold (−73 °C) solution of LDA·THF (200 mL of 1.5 M in cyclohexane, 0.3 mol) in THF (100 mL) was added anhydrous CH_3CN (15.7 mL, 0.3 mol) dropwise over 50 min. After the mixture stirred for 35 min, a solution of the ketone (**6**, 35 g, 0.22 mol) in THF (50 mL) was added dropwise at a rate such that the internal temperature remained below −65 °C. After the addition was complete, the cooling bath was removed and the mixture allowed to warm to 0 °C. The amber-colored solution was poured into 1 M HCl (300 mL) and then extracted with toluene (2 × 100 mL). The organics were dried (Na_2SO_4/$MgSO_4$) and the solvents removed in vacuo, leaving an amber oil (40.2 g). The oil was dissolved in toluene (100 mL) and treated with *p*-TsOH·H_2O (3.0 g). The solution was heated to reflux, and water was removed using a Dean−Stark trap. After 3 h, an additional 1.0 g of *p*-TsOH·H_2O was added and the mixture heated at reflux for 3 h, at which time GC analysis indicated that the dehydration was complete. The organics were washed with water (100 mL), 5% Na_2CO_3 (2 × 100 mL), water (100), and brine (100 mL). After the organics were dried (Na_2SO_4), the solvents were removed in vacuo, leaving a dark brown liquid. Distillation through a 10 cm Vigreux column provided the nitrile isomers **13** as a pale yellow liquid (33.5 g, 83%, bp 110 °C at 0.4 mmHg): ^{1}H NMR ($CDCl_3$) 1.27 (s, CH_3), 1.53 (s,CH_3), 2.91 (s, CH_3), 2.99 (s, CH_3), 5.20 (s, CH), 5.70 (s, CH), 7.27−7.5 (m, Ar H's and one olefinic H), 8.36 (d, J = 7.4 Hz,1 H); ^{13}C NMR (CDCl3) 26.9, 28.6, 43.8, 44.5, 46.0, 48.1, 84.5, 84.9, 117.4, 117.8, 121.4, 124.9, 125.3, 125.4, 127.0, 131.5, 131.7, 136.2, 137.4, 145.5, 146.4, 173.4, 173.7; GC analysis t_R = 5.15 (41) and t_R = 5.17 (59); MS (GC) of the isomers are virtually identical 183 (M^+, 30), 168 (100); Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.45. Found: C, 85.46; H, 7.29; N, 7.50.

2-(2,2-Dimethyl-1-indanylidene)acetonitrile (15) via the KOH acetonitrile method. A nitrogen-purged 3-L three necked round-bottom flask with thermowell was fitted with a mechanical stirrer, septum, and condenser with nitrogen inlet. To the flask was added acetonitrile (604 mL) and powdered KOH (88 g, ∼1.33 mol) causing a mild exotherm. After the mixture cooled to ambient temperature, a solution of the ketone **2** (100 g, 0.625 mmol) in acetonitrile (200 mL) was added, resulting in a black-purplish mixture. The dark mixture was allowed to stir at reflux overnight. The mixture was cooled to room temperature, and water (75 mL) was added. The solvent was removed in vacuo, leaving a dark liquid. The liquid was diluted with H_2O (400 mL) and extracted with toluene (3 × 200 mL). The organic phase was concentrated on the rotovap, leaving a black oily tar. Kugelrohr distillation provided the crude product (bp 128 °C, 1.6 mmHg) as a pale yellow liquid. Distillation through a 10 cm Vigreux column afforded unreacted ketone and then the product **15** (bp 110 °C at 0.4 mmHg) as a clear yellow liquid (58.1 g, 51%): GC analysis, t_R = 5.17 min (96%).

2-(2,2-Dimethyl-1-indanyl)acetonitrile (16). A solution of the olefin isomers **15** (20.8 g, 0.114 mol) in ethanol (100 mL) were added to a nitrogen-purged Parr reactor containing 10% Pd/C (1.0 g) and water (15 mL). The mixture was hydrogenated with good stirring at 200 psi for 16 h. The slurry was filtered through Celite and the pad washed with ethanol (25 mL). The solution was concentrated in vacuo and the residue partitioned between CH_2Cl_2 (60 mL) and water (40 mL). The organics were dried (Na_2SO_4) and the solvents removed on the rotovap, leaving a yellow liquid. Drying to a constant weight (0.5 mmHg/room temperature) afforded **16** as a pale yellow liquid (21 g, 100%): ^{1}H NMR-($CDCl_3$) 1.04 (s, 3H), 1.25 (s, 3H), 2.55 (d, J = 7.2 Hz, 2H), 2.77 (2, 1H), 3.08 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 17.8, 22.6, 28.1, 43.0, 46.5, 50.4, 119.2, 123.8, 124.7, 126.4, 127.2, 141.9, 143.1; Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 83.93; H, 8.22; N, 7.22.

2-(2,2-Dimethyl-1-indanyl)-1-cyanoethanal (17). To a cold (−73 °C) solution of LDA·THF (180 mL of 1.5 M in cyclohexane, 0.27 mol) in THF (180 mL) was added a solution of **16** (22.8 g, 0.123 mol) in THF (25 mL) dropwise at a rate such that the internal temperature did not exceed −66 °C. After the addition was complete, the clear brown solution was allowed to stir for ∼30 min. Ethyl formate (14.5 mL, 0.179 mol) was added dropwise such that the internal temperature did not exceed −45 °C. The cooling bath was removed, and the mixture was allowed to warm to room temperature. Water (180 mL) was added and then most of the THF removed on the rotovap. The residue was diluted with water, and the resulting aqueous slurry was extracted with toluene (2 × 180 mL). The aqueous solution was chilled in an ice bath and taken to pH 3 by the addition of concentrated HCl. The resulting solid was filtered and washed well with water. Drying to a constant weight provided **17** as a pale yellow solid (22.4 g, 85%) which was 97+% pure via GC analysis. Recrystallization of a small sample from toluene afforded **17** as a white crystalline solid: mp 144−46 °C; ^{13}C NMR (DMSO-d_6) shows the material to be a ∼1/1 mixture of enol tautomers 23.7, 27.5, 28.4. 44.8, 45.5, 46.2, 46.5, 49.9, 54.3, 86.1, 88.9, 117.8, 120.8, 124.5, 124.7, 124.8, 126.3, 126.4, 126.9, 127.0, 142.3, 142.8, 142.9, 143.1, 158.7, 159.5; MS (GC), the isomers are inseparable, 213 (M^+, 15), 198 (10), 145 (100), 128 (25), 115 (45).

Ethyl *E*- and *Z*-2-(2,2-Dimethyl-1-indanylidene)acetate (13). To a cold (−70 °C) solution of LDA·THF (100 mL of 1.5 M in cyclohexane, 0.15 mol) in THF (50 mL) was added

anhydrous ethyl acetate (14.7 mL, 0.15 mol) dropwise at a rate such that the internal temperature did not exceed −67 °C. After the mixture stirred for 25 min, the ketone **2** (22 g, 0.138 mol) was added in portions at a rate such that the internal temperature remained below −64 °C. The dark solution was stirred in the cold for 1 h and then allowed to warm slowly to −20 °C. To the mixture was added saturated aqueous NH_4Cl (75 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (50 mL), and the combined organics were dried (Na_2SO_4/$MgSO_4$). The solvents were removed in vacuo, leaving a light amber oil. The oil was dissolved in toluene (50 mL) and treated with p-TSOH·H_2O (3 g). The solution was heated to reflux using a Dean−Stark trap to remove water. The mixture was refluxed for ∼2 h at which time GC analysis indicated the dehydration was complete. The dark amber mixture was cooled to room temperature and then extracted with 5% Na_2CO_3 (3 × 75 mL) and water (2 × 75 mL). After drying (Na_2SO_4) the solvents were removed in vacuo, leaving a dark amber oil. Distillation through a 10 cm Vigreux column afforded the olefin isomers **13** as a yellow liquid (25.2 g, 79%, bp 132−35 °C at 1.4 mmHg); ^{1}H NMR($CDCl_3$); MS (GC) isomers are inseparable, 230 (M^+, 50), 215 (10), 185 (40), 169 (20), 157 (100), 142 (85).

2-(2,2-dimethyl-1-indanyl)acetate (18). The procedure described for the preparation of **16** was utilized. The ester **18** was obtained as a clear colorless liquid (4.8 g, 95%): ^{1}H NMR($CDCl_3$); MS (GC) 232 (M^+, 15%), 158 (95%), 143 (100%).

4-Amino-(2,2-dimethyl-1-indanyl)pyrimidine (19) from 6. A 500 mL three-neck round-bottomed flask equipped with a mechanical stirrer (glass paddle), two dry ice condensers, and a nitrogen inlet was purged with nitrogen for 30 min. The condensers were charged with dry ice/ethanol, and the vessel was cooled in a dry ice/ethanol bath. Ammonia (175 mL, ∼135 g) was slowly condensed into the reactor, and then one of the dry ice condensers was replaced with a stopper. Initially, four pieces of sodium metal (approximately 0.2 g size) were added to the reactor, causing the solution to turn to a deep blue color. Approximately 50 mg of Fe(NO_3)$_3$·9H_2O was added as a catalyst. After the solution turned to a grayish mixture, more sodium metal (5.75 g total, 0.25 mol) was added in portions, while the pot temperature was maintained at −33 to −35 °C (addition time was 50 min). After the addition was completed and the reaction mixture turned gray, stirring was continued for an additional 15 min at −35 °C. The stopper was replaced with a rubber septum, and anhydrous toluene (50 mL) was added via a syringe and needle. Anhydrous acetonitrile (9.44 g, 12 mL, 0.23 mol) was then added dropwise via a syringe and needle over a period of 5 min. The reaction was stirred for an additional 30 min while the temperature of −35 °C was maintained.

A solution of 2,2-dimethyl-1-indanone (**6**, 31.6 g, ∼95%, 0.187 mol) in anhydrous toluene (40 mL) was added to the reaction mixture (via a syringe and needle) over a period of 15 min. After the mixture stirred at −35 °C for 30 min, cooling was discontinued, and the reaction was slowly warmed to 25 °C using a warm water bath to distill ammonia. Stirring was stopped to allow the black and gray insoluble materials to settle to the bottom of the reactor. The reaction solution was transferred via a cannular tube to a 1-L three-necked round-bottomed flask equipped with a mechanical stirrer, ice bath, and a thermometer. The flask contained a vigorously stirred solution of 3 N HCl (250 mL) pre-cooled to −8 °C. The rate of transfer was such that the quenched mixture was maintained at or below 0 °C. The reactor was rinsed with 50 mL of anhydrous toluene and transferred to the quenched mixture. In a separatory funnel the aqueous phase was discarded, and the toluene phase was washed with water (2 × 100 mL). The toluene phase was then charged into a 500 mL three-necked round-bottomed flask equipped with a mechanical stirrer, a thermometer, a heating mantle, and a Dean−Stark trap with a cold water condenser. The toluene solution was dried azeotropically until the pot temperature reached 110 to 114 °C at which time heating was stopped and one drop of concentrated H_2SO_4 (∼20 mg) was added. Heating and azeotropic drying was continued, and after 25 min, GC analysis indicated the dehydration reaction was complete. The reaction was cooled to ∼30 °C and transferred to a separatory funnel. The toluene solution was washed with water (2 × 100 mL) and then transferred back into the reactor. The toluene solution was dried azeotropically and distilled until the total in-pot volume was ∼70 mL. The yellow toluene solution of **15** was allowed to cool to room temperature under a slight positive pressure of nitrogen.

A 500 mL three-necked round-bottomed flask equipped with a mechanical stirrer (glass paddle), 2 dry ice condensers, and a nitrogen inlet was purged with nitrogen for 30 min. The reactor was charged with sodium metal (8.9 g, 0.387 mol). The condensers were charged with dry ice/ethanol, and the vessel was cooled in a dry ice/ethanol bath. Ammonia (250 mL, ∼193 g) was slowly condensed into the reactor affording a deep black-blue solution. One of the dry ice condensers was replaced with a rubber septum. The yellow solution of **15** from the above reaction was added via a syringe and needle while maintaining a pot temperature of −33 °C to −40 °C. The solution retained its blue-green color. (Note: If the solution is a reddish orange color, then more sodium metal is required, and the stoichiometry of the remaining reagents are adjusted accordingly). The mixture was stirred for 5 min and anhydrous methylformate (14.1 g, 14.4 mL, 0.21 mol) was added dropwise via a syringe needle over a period of 3 min. The pot temperature was maintained at less than −30 °C. After over half of the methylformate solution was added, the reaction solution turned from blue to an orange-yellow color. After few minutes, the solution thickened to a pale yellow slurry with a consistency of thin pancake batter. The yellow slurry was stirred at −30 to −40 °C for 15 min, and formamide (75 mL) was slowly added while allowing the NH_3 to distill. The pot temperature had increased to −22 °C at the end of addition with most of the paste being converted to an orange solution. NH_4Cl (20.0 g, 0.37 mol) was cautiously added, turning the solution to a yellow color with some precipitate. The reactor was fitted

with a stopper, a short-path distillation head, and a nitrogen inlet with the exit tube in a water trap. The reaction mixture was heated slowly to 185 °C while the distillate was removed. As the pot temperature increased and distillate was removed, a precipitate began to form, and the mixture became a slurry as the pot temperature reached 185 °C. The reaction was held at 185 °C for 4 h at which time GC analysis indicated that the reaction was mostly completed. The brown mixture was cooled to 120 °C, toluene (45 mL) and water (95 mL) were added. The mixture was cooled to room temperature with vigorous stirring and stirred at room temperature for 150 min. The crude product (tar-like clumps) was collected in a sintered glass funnel via filtration. The mother liquor was returned to the reactor to rinse the crystals that had adhered to the walls of the reactor. The reactor was then rinsed with 50 mL of toluene which was used to slurry the crude clumps in the funnel into a homogeneous mixture, and this mixture was filtered. The wet cake was slurried and washed with an additional portion of 75 mL of toluene. The cake was washed with water (100 mL) and dried in a vacuum oven at 50 °C overnight. The off-white solid (28.9 g) assayed at 98.2%, affording an isolated yield of 63.5% from the ketone **6**. Treatment of a small sample with ethanol/charcoal followed by recrystallization from toluene provided an analytical sample: mp 162−164 °C; ^{13}C NMR ($CDCl_3$) 24.0, 24.6, 29.9, 45.3, 45.7, 47.1, 47.9, 53.5, 58.8, 115.6, 116.8, 124.8, 125.1, 125.4, 125.7, 126.7, 127.0, 127.2, 127.9, 140.6, 142.6, 143.2, 143.4, 155.8, 156.4, 157.2, 157.6, 161.7, 162.2; ^{1}H NMR not listed due to the spectral complexity caused by amine/imine tautomers;[20] MS (GC) 239 (M^+, 75%), 224 (100%), 196 (20%). Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.51; H, 7.37; N, 17.48.

4-Amino-(2,2-dimethyl-1-indanyl)pyrimidine (19) from 17. The enol-nitrile isomers **17** (1.0 g, 4.69 mmol) and ammonium chloride (1.0 g, 18.7 mmol) were slurried in formamide (50 mL) and heated to 160 °C under nitrogen. After 2.5 h at this temperature, GC and GC/MS analyses indicate that all of **17** had been consumed and a 94/5 mixture of isomers **20**/**21** had resulted. Continued heating at 175 °C for 1 h showed little increase in the amount of **19**. The mixture was warmed to 190 °C and held there for 3 h at which time all of the **20** and **21** had been consumed and **19** was the major component as determined via GC/MS analysis. The dark reaction mixture was cooled to room temperature, and then formamide (43 mL) was removed via distillation at 0.1 mmHg/65−75 °C. The dark residue was triturated with water (50 mL) containing K_2CO_3 (1.0 g). The resulting dark solid was collected on a filter and washed with water. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the dark solid then dissolved in the EtOAc extracts. This solution was filtered through a plug of silica gel (~30 g), and the pad was rinsed with EtOAc (150 mL). The filtrates that contained product (by TLC analysis) were combined and the solvents removed on the rotovap, leaving a tan solid. Drying to a constant weight provided the product as a beige solid (805 mg, 72%): mp 156−59 °C; MS (GC) as above.

5-(2,2-Dimethyl-1-indanyl)-4(3H)pyrimidinone (22). Compound **19** (43.9 g, 0.184 mol based on 77.4 g of wet cake which assayed at 56.7%), water (110.3 g), and 37% hydrochloric acid (294.4 g) were heated at 110−116 °C for 21 h. The thick slurry was cooled to room temperature and was filtered. The solids were washed with water (150 mL), followed by toluene (150 mL). After drying under vacuum at 75 °C, the light tan solids (49.5 g) assayed at 86.6% relative to the free base of **22**, giving a calculated yield of 42.9 g (97%) of **22**: ^{1}H NMR (DMSO-d_6) 10.62 (2 H, br s), 9.10 (1 H, s), 7.29−7.01 (5 H, m), 4.26 (1 H, s), 2.84−2.69 (2 H, dist q), 1.16 (3 H, s), 0.84 (3 H, s); mp 258−259 °C. A small sample was converted to the free base by partitioning between aqueous K_2CO_3 and EtOAc. An analytical sample was obtained by recrystallization from ethanol/water: mp 138−139 °C; Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.81; H, 6.92; N, 11.45.

2,2-Dimethyl-1-(4-methylthio-5-pyrimidinyl)indane (1). Compound **22** (24.9 g, 0.104 mol based on 28.9 g of solids which assayed at 86.3%), 1,2-dichloroethane (100 mL), thionyl chloride (25 g), and dimethylformamide (1.5 g) were heated to reflux for 7 h. The solution was cooled to room temperature, and water (50 mL) was added. The mixture pH was adjusted to approximately 7.5 by adding 8.2 g of potassium carbonate. The layers were separated. To the organic layer were added, in shots over several hours, water (90 mL), sodium thiomethoxide (24.96 g), 1.0 g of benzyltriethylammonium chloride, and 20% aqueous sodium hydroxide (5.6 g). After the reaction showed 87% conversion by area %, the layers were separated, and the organic layer was re-extracted with water (50 mL). The combined aqueous layers were extracted with 1,2-dichloroethane (30 mL). To the combined organic layers were added another 0.3 g of benzyltriethylammonium chloride and 2.08 g of sodium thiomethoxide. After stirring 3 days, the mixture showed about 91% conversion. The layers were separated, and the aqueous layer was reextracted with 1,2-dichloroethane (30 mL). The combined organic layers were concentrated to a brown oil. The oil was diluted with acetonitrile (50 mL), giving solids, followed by water (50 mL). The slurry was filtered, washing the solids with water (25 mL). The solids were recrystallized from hot acetonitrile (50 mL), adding water (50 mL) after crystals formed. The slurry was filtered, and the solids were washed with 25 mL of city water. The solids were recrystallized again from hot acetonitrile (50 mL) and water (20 mL). The slurry was filtered and the solids were washed with water (20 mL). The solids were dried under vacuum at 75 °C, giving 18.1 g (65%) of light tan granules of pure **1**.

***E*- and *Z*-2-(2,2-Dimethyl-1-indanyl)-2-cyanoethenamine (20).** A solution of nitrile **17** (1.0 g, 4.7 mmol) was dissolved in ethanol (14 mL) and treated with NH_4Cl (20 mg). The solution was heated at reflux under an atmosphere of NH_3 (balloon) until the reaction was judged to be complete via GC analysis (4.5 h). After cooling to room temperature the precipitate was collected and washed with a little ethanol.

(20) A note added in proof: compound **19** prepared by the oxidation of **1** to the corresponding methy sulfone followed by displacement with ammonia, displayed spectral properties identical to material prepared by the cyclization method.

The material was dried to a constant weight at 0.5 mmHg/room temperature providing **20** as a fluffy white solid (550 mg): GC analysis indicated a 96(t_R = 7.04)/4(t_R = 7.64) mixture of olefin isomers; MS (GC) for each isomer gave almost identical spectral data, 212 (M^+, 85), 197 (30%), 180 (35), 170 (100), 129 (70); ^{1}H NMR (major isomer, DMSO-d_6) 0.86 (s, 3H), 1.10 (s, 3H), 2.66 (bs, 2H), 3.33 (s,1H), 6.35 (d, J = 10.8 Hz, 2H), 6.82 (t, J = 10.8 Hz, 1H)7.05−7.17 (m, 4H); ^{13}C NMR (major isomer, DMSO-d_6) 23.5, 27.3, 45.1, 46.0, 56.4, 73.3, 120.0, 124.3, 124.4, 126.0, 126.5, 142.0, 143.9, 150.2; Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.50; H, 7.80; N, 12.95.

***E*- and *Z*-2-(2,2-Dimethyl-1-indanyl)-2-cyano-*N*-formylethenamine (21).** A slurry of the amino nitriles **20** (500 mg, 2.4 mmol) in toluene (8 mL) was treated with acetic-formic mixed anhydride[21] (400 mg, 4.5 mmol) and the mixture warmed to 90 °C. After 30 min, all solids had gone into solution, and GC analysis indicated that 5% of **20** remained. Additional mixed anhydride (75 mg) was added and the mixture kept at 90 °C for 45 min. The reaction was cooled to room temperature, and the volatiles were removed on the rotovap, leaving a pale yellow oil. Drying overnight at 1 mmHg/room temperature provided isomers **21** as a pale yellow solid: GC analysis indicated an 83(t_R = 7.57)/14(t_R = 7.91) mixture of isomers **21** along with 1.3% of the *N*-acetylated analogue; MS (GC) of each of the isomers gave almost identical spectral data, 240 (M^+, 60), 195 (35), 180 (100); ^{1}H NMR (major isomer, $CDCl_3$) 1.03 (s, 3H), 1.20 (s, 3H), 2.81 (ABq, J = 9.8, 15.5 Hz, 2H), 3.48 (s, 1H), 7.13−7.24 (m, 4H), 7.49 (d, J = 11.6 Hz, 1H), 8.20 (s, 1H), 8.68 (bd, J = 11.6 Hz, 1H); Anal. Calcd for $C_{15}H_{17}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.03; H, 6.90; N, 11.39.

(21) For the preparation of acetic−formic mixed anhydride see: Fieser, M.; Fieser, L. *Reagents for Organic Synthesis*; Wiley & Sons: New York, 1969; Vol. 2, p 10.

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