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Full Papers

Development of a Practical Synthesis of the Progesterone Receptor Antagonist 4-{[3-Cyclopropyl-1-(mesylmethyl)-5-methyl-1H-pyrazol-4-yl]oxy}-2,6-dimethylbenzonitrile

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Abstract:

The development and implementation of a scaleable process for the manufacture of the nonsteroidal progesterone receptor antagonist 8 is described. Key aspects of the synthesis include (i) a telescoped chlorination−etherification sequence to prepare diketone 4 and (ii) separation of pyrazole regioisomers 6 and 7 through formation of their hydrogen sulfate salts and selective crystallization, followed by oxidation to 8.

Introduction

The use of progesterone receptor (PR) antagonists for the treatment of a variety of progesterone-related diseases and disorders is of considerable interest, and recent studies have indicated that PR antagonists could have potential applications in the treatment of endometriosis and uterine fibroids.[1] At present, RU-486 (mifepristone) is the only PR antagonist approved for clinical use and then only for short duration. It is an 11β-substituted steroid and displays potent antagonist activity at other steroidal receptors, in particular the glucocorticoid receptor (GR)[2,3] and the androgen receptor (AR).[4] As part of a program to identify nonsteroidal PR antagonists, 4-{[3-cyclopropyl-1-(mesylmethyl)-5-methyl-1H-pyrazol-4-yl]oxy}-2,6-dimethylbenzonitrile **8** emerged as a selective PR antagonist[1] and was advanced into clinical development. In order to support the proposed clinical development program, bulk supplies of **8** were required, and herein we describe the development of a practical, scaleable route to **8**.

The medicinal chemistry route to **8** is shown in Scheme 1. This route was designed in order to facilitate late-stage incorporation of structural diversity on the pyrazole side chain; however, a major drawback is that alkylation of unsubstituted pyrazole **5** proceeds with poor selectivity, and the resulting regioisomeric mixture has to be separated by chromatography.

While this process is clearly suboptimal since approximately half the material is lost at the penultimate stage, an initial assessment of alternative routes (largely based on retrosynthetic analysis, coupled to a thorough literature search) failed to identify a more convergent option that could be developed in the available time frame. Given the urgent need for material for clinical development, the decision was made to develop this route. Key points that needed to be addressed prior to scale-up were:

- low overall yield of the chlorination and ether formation steps (Scheme 1, steps a and b; 35%)
- poor regioselectivity of the alkylation of pyrazole **5** (~1.5:1 mixture obtained)
- inefficient chromatographic separation of pyrazole regioisomers **6** and **7**.

The first step consists of the chlorination of the readily available diketone **1**[5] with *N*-chlorosuccinimide (NCS) and chlorotrimethylsilane (TMSCl) in dichloromethane (DCM).[1] The major side product observed in this reaction was the dichloride **9** (Figure 1), and the formation of this was minimised by controlling the temperature (0−5 °C) and adding one equivalent of the solid chlorinating reagent slowly over approximately 1 h.

For the small-scale campaigns this process worked well; however, for larger campaigns the slow addition of a solid over an extended period was impractical, so this was changed to the slow addition of a solution of NCS in DCM to the reaction mixture, giving comparable levels of dichloride (6−8%) to the previous method. One drawback of this was the increased reaction volume due to the low solubility of NCS in DCM.

In an attempt to overcome the problem of high dilution and low throughput, the chlorination reaction was screened in a range of alternative solvents, from which acetonitrile emerged as the only viable replacement. Since chloro-diketone **2** is a lachrymatory oil, our preferred option was not to isolate this

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(1) (a) Bradley, P. A.; Dack, K. N.; Johnson, P. S.; Skerratt, S. E. U.S. Patent Application US 2007/0105909 A1, 2007. (b) Dack, K. N.; Gibson, K. R.; Skerratt, S. E. Patent Application WO 2008/047224 A1, 2008.
(2) Moguilewsky, M.; Philibert, D. *J. Steroid Biochem.* **1984**, *20*, 271.
(3) Teutsch, G.; Ojasoo, T.; Raynaud, J. P. *J. Steroid Biochem.* **1988**, *31*, 549.
(4) Song, L.-N.; Coghlan, M.; Gelmann, E. P. *Mol. Endocrinol.* **2004**, *18*, 70.
(5) Cannon, G. W.; Whidden, H. L. *J. Org. Chem.* **1952**, *17*, 685.

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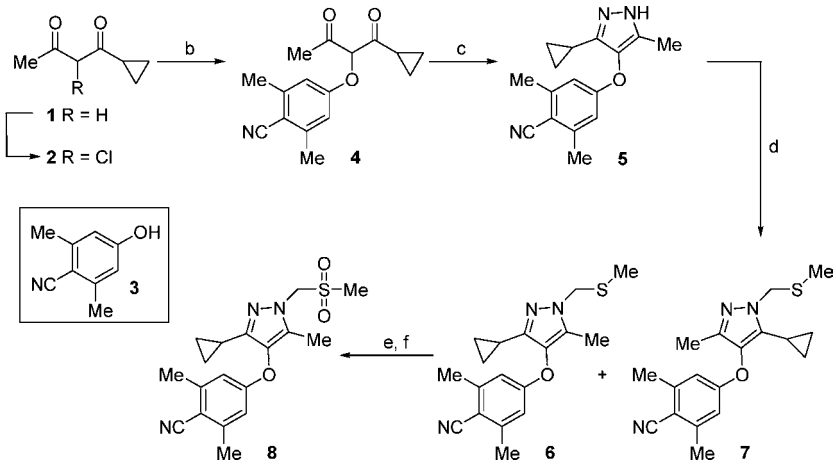
Scheme 1. **Medicinal chemistry route**[a]



[a] *Reagents and Conditions*: (a) NCS, TMSCl, DCM, 0−5 °C; (b) **3**, Cs_2CO_3 acetone, reflux. 35% from **1**; (c) $H_2NNH_2 \cdot H_2O$, AcOH, 25 °C, 95%; (d) $ClCH_2SCH_3$, KOtBu, 1,2-DME, 0 → 25 °C; (e) silica gel chromatography, 48%; (f) Oxone, MeOH, H_2O, 25 °C, 75%.

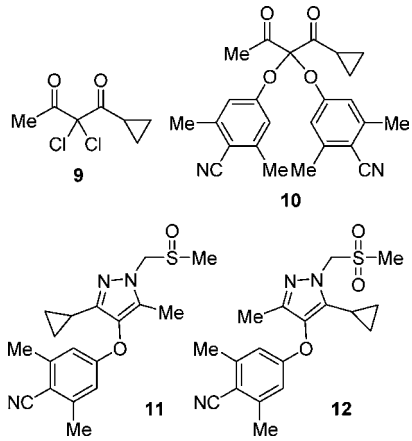


Figure 1. **Process-related impurities 9−12.**

compound and simply telescope it into the ether formation in order to minimise the risk of operator exposure. However, the byproduct succinimide also reacts with the chloro-diketone **2** in the ether formation step; therefore, it was essential to remove the succinimide from the crude chloro-diketone **2** prior to running the etherification. The easiest way to achieve this was through a series of aqueous washes; as a result the use of the water-miscible acetonitrile would be problematic, and thus, despite the nonideal conditions, the decision was made to conduct the chlorination reaction in DCM.

During the development of the etherification (Scheme 1, step b), the key priority was to identify a suitable crystallisation solvent for the phenoxy diketone **4** and, if possible, to identify more practical reaction conditions. Isopropanol (IPA) was quickly identified as an excellent crystallisation solvent, consistently giving high-quality product and purging residual starting materials and minor impurities. During some of the larger-scale lab runs, small amounts of diphenoxy-diketone **10** (Figure 1) arising from reaction of phenol **3** with dichloride **9** (Figure 1) were observed in the isolated product (3−5%). This appeared to be related to an extended granulation period postcrystallisation, and by limiting this to less than 2 h this impurity was not observed during the pilot-plant campaign. In any case, the presence of a small amount of **10** is not of concern as it is readily removed during the crystallisation of the pyrazole **5**.

A screen of solvent and base combinations identified MeCN/iPr_2NEt as the ideal reagents for the etherification, giving good conversion and a clean reaction profile. Once the reaction was complete, solvent exchange to IPA afforded the product **4** in an acceptable 60% yield from diketone **1** on multikilogram scale.

The unsubstituted pyrazole **5** was originally prepared by condensation of diketone **4** with hydrazine in acetic acid at ambient temperature. While the reaction worked well, the use of acetic acid as solvent and the resulting laborious workup were not ideal for scale-up. Since pyrazole **5** is soluble in most solvents (apart from water and heptane), crystallisation options were limited. Fortunately, the reaction proceeded efficiently in a range of solvents in the presence of one equivalent of acetic acid, and after some experimentation, it was found that slow addition of water to an ethanolic solution of pyrazole **5** gave a reliable and robust crystallisation. It was important to add the water slowly to prevent the product oiling out of solution. This modified process worked well in the plant, affording an excellent 93% yield of the desired pyrazole **5**.

The key step in the reaction sequence was the alkylation of pyrazole **5** with chloromethyl methyl sulfide, to give a mixture of the two regioisomeric sulfides, **6** and **7**. A comprehensive range of bases and solvents was screened in an attempt to improve the regioselectivity of this reaction, but with limited success. The highest selectivity obtained was ∼2:1 (in favor of **6**) using Cs_2CO_3 and KI in DMF; however, the reaction stalled at only ∼10% conversion. Most reactions in this screen failed to reach full conversion, and given that the differences in selectivity were fairly small, reactions that gave full conversion were prioritised in order to maximise the yield of **6**.

The best compromise between reactivity and selectivity was found to be the original medicinal chemistry conditions, KOtBu in DME, which gave full conversion and a 1.5:1 mixture of isomers, favoring the desired **6**. In addition, a range of Pummerer-type reaction conditions[6,7] were also investigated;

(6) Dabbagh, H. A.; Bagheri, A. *J. Chem. Res.* **2005**, 202.

of these only hexamethyldisilazane in hot DMSO[7] yielded significant amounts of product, unfortunately, as a 1:1 mixture of **6** and **7**. Since this offered no advantage over the alkylation method and gave lower selectivity, it was not investigated further. Having failed to identify conditions that provided significantly better regioselectivity for the alkylation, the focus then shifted to finding a more efficient separation of the two isomers **6** and **7**.

During the initial campaigns, the crude mixture of **6** and **7** after workup and concentration was loaded directly onto a silica gel column for purification and separation. While this approach did work, it was not ideal for scale-up as there were volatile sulfur residues that would need to be scrubbed during the concentration, the residual oil was malodorous and unpleasant to handle, and the high impurity burden resulted in an inefficient chromatographic separation necessitating the use of large amounts of silica gel and solvent.

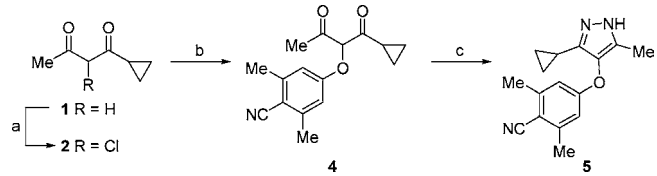
A selection of strong acids was screened against the crude reaction mixture to see if any crystalline salts were formed,[8] and solid residues were observed with both methanesulfonic and sulfuric acids in ethyl acetate. However, when the methanesulfonic acid process was repeated, the solid was found to be derived from an unidentified impurity present in the crude material and not related to the products **6** and **7**. Fortunately, in the case of the sulfuric acid salt, the isolated solid was a mixture of the isomeric pyrazole salts **6a** and **7a**.

The sulfate salt process was then scaled up, and the isolated solid consistently afforded about a 4:1 mixture of the two isomers, favoring the desired **6a**. Initially, the salt was prepared in ethyl acetate; however, this was changed to isopropyl acetate as this solvent has greater stability under acidic conditions. No change in the isolated yield or isomer ratio was observed compared to those from the ethyl acetate process. An added bonus of isolating the salt at this point was that the majority of the noxious byproducts remained in the liquors and were easily contained and disposed of. Since the product salt was enriched in the desired isomer (**6a**) and the bulk of the impurities had been removed, a significantly more efficient chromatographic separation was developed, but was still not ideal. After screening a range of solvents, we found that reslurrying the crude salt in acetonitrile gave an efficient purge of the unwanted isomer **7a** with good recovery of material (~40% overall yield of pure **6a** from pyrazole **5** on lab scale).

However, when this process was scaled up to 700 g input pyrazole **5**, the alkylation reaction failed to reach completion, despite the use of excess reagents (2.2 equiv of chloromethyl methyl sulfide and 2 equiv of KOtBu), necessitating further investigation prior to the plant campaign.

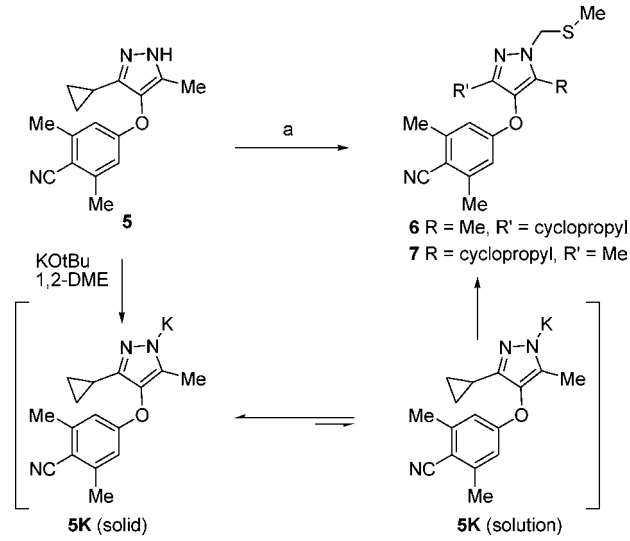
The reaction was carried out by first generating the potassium anion **5K** by addition of a solution of pyrazole **5** in DME to a slurry of KOtBu in DME (Scheme 3). Once the anion had formed, the electrophile was added to the resulting slurry. Initial experiments showed that the problem was linked to the low

Scheme 2. **Synthesis of unsubstituted pyrazole 5**[a]



[a] *Reagents and Conditions*: (a) NCS, TMSCl, DCM, 0−5 °C; (b) **3**, iPr_2NEt, MeCN, reflux, then iPrOH. 60% from **1**; (c) $H_2NNH_2 \cdot H_2O$, AcOH, EtOH, 25 °C, then H_2O, 93%.

Scheme 3. **Alkylation of pyrazole 5**[a]



[a] *Reagents and Conditions*: (a) (i) KOtBu, 1,2-DME, 0 °C to RT; (ii) $ClCH_2SMe$, 1,2-DME.

solubility of **5K** in DME, and resulted in the working hypothesis that, as the electrophile is added, it rapidly consumes the small amount of **5K** present in solution, and before any more **5K** dissolves, the highly reactive chloromethyl methyl sulfide is consumed through undesired side reactions. Based on this hypothesis, the obvious solutions were to either increase the amount of anion in solution by adding a better solvent or to reduce the amount of electrophile present during the reaction by dosing it in more slowly.

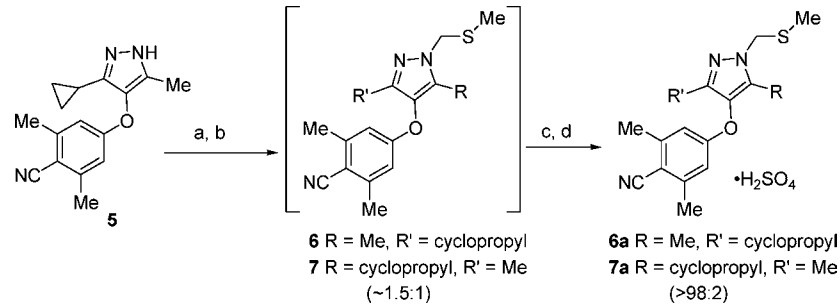
Since the initial screening work had identified DME as one of the better solvents for this reaction in terms of selectivity and conversion, the use of a cosolvent (DMF, NMP, DMPU) to improve the solubility of anion **5K** in DME was briefly examined. While the addition of a cosolvent did improve the solubility of the anion, this had very little impact on the reaction profile, adversely affected the workup, and was not pursued. Gratifyingly when the electrophile was added over an extended period, the process worked as well as before on a reasonably large lab scale.

On the basis of this successful lab trial, the process was then scaled up into the plant. To our delight, simply by slowing down the electrophile addition rate (to 90 min in this case), the pyrazole **5** was completely consumed, yielding the usual ~1.5:1 mixture of isomers **6** and **7**. The reaction mixture was converted through to the corresponding hydrogen sulfate salts **6a** and **7a**, and after reslurrying in acetonitrile, almost pure **6a** was isolated

(7) Janzen, A. F.; Lypka, G. N.; Wasylishen, R. E. *Can. J. Chem.* **1980**, *58*, 60.

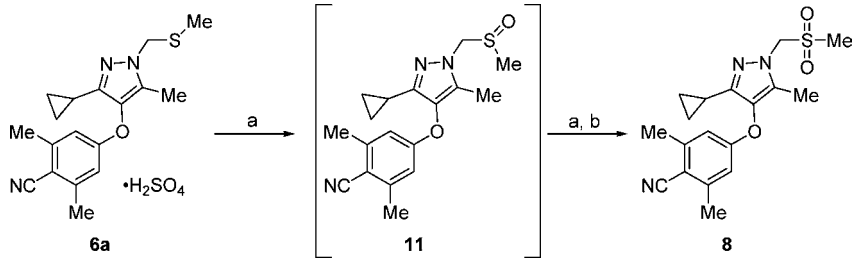
(8) A literature search indicated that pyrazole salts with strong acids were known, so the following acids were screened in a selection of solvents: hydrochloric, hydrobromic, sulfuric, phosphoric, *p*-toluenesulfonic, benzenesulfonic, methanesulfonic, and ethylenedisulfonic.

Scheme 4. **Synthesis and purification of hydrogen sulfate salt 6a**[a]



[a] *Reagents and Conditions*: (a) KOtBu, 1,2-DME 0 °C to RT; (b) $ClCH_2SMe$, 1,2-DME (slow addition); (c) H_2SO_4, iPrOAc; (d) MeCN reslurry, 37% overall.

Scheme 5. **Oxidation of pyrazole salt 6a**[a]



[a] *Reagents and Conditions*: (a) Oxone, EtOAc, water; (b) IPA, 75%.

in 37% overall yield from pyrazole **5**. HPLC analysis indicated that there was 1.7% of the regioisomer **7a** present after the reslurry.

Oxidation of sulfide **6** to sulfone **8** was initially conducted using Oxone in aqueous methanol.[9] While this process worked reasonably well, the reaction was heterogeneous and posed a risk of inconsistent performance as it was scaled up.[10] In this instance, a homogeneous process would be preferable. Given the low cost, ready availability on scale, and proven functional group compatibility, the use of Oxone for the oxidation was prioritised.

Since Oxone is virtually insoluble in organic solvents, the use of biphasic mixtures was explored. Sulfone **8** is soluble in ethyl acetate and isopropyl acetate, so these were examined in conjunction with aqueous Oxone solutions. Ethyl acetate performed significantly better than isopropyl acetate in this oxidation, and so was selected for further development. An added advantage of this biphasic process was that the hydrogensulfate salt **6a** could be used directly, removing the need to free-base the material. The main challenge was to drive the reaction to completion. Initial oxidation to the sulfoxide **11** proceeded rapidly, but oxidation of the sulfoxide **11** to the desired sulfone **8** proceeded extremely slowly, particularly as the reaction was scaled up. In many cases the reaction stalled completely and could only be restarted by the addition of fresh oxidant solution.

As a result, a process was developed wherein the oxidant was dosed in multiple charges to the reaction mixture, with testing in between each charge until reaction completion was achieved. The use of phase-transfer catalysts to accelerate the oxidation was examined, but without any success.

Once the reaction was complete, the aqueous phase was discarded, and the final product **8** was crystallised in excellent purity by solvent exchange from ethyl acetate to IPA. Controlling the level of regioisomer **7a** present prior to the oxidation proved to be critical; if this was present at <2%, the regioisomeric sulfone **12** (Figure 1) was adequately controlled to acceptable levels in **8**. Interestingly, higher initial levels of **7a** led to a relative increase in the level of **12** in the final product **8**, indicative of some enrichment of this impurity during processing and crystallisation.

This procedure was then scaled up into the pilot plant. On this scale, the process required five separate charges of aqueous Oxone to drive the reaction to completion; however, the isolation proceeded smoothly to give the desired product in an acceptable 75% overall yield.

Given the poor efficiency of this oxidation process (in total, 10 equiv of the oxidant $KHSO_5$ were required, when only 2 are theoretically needed) the use of alternative oxidants has been briefly examined. Both sodium tungstate/hydrogen peroxide[11] and peracetic acid have given promising preliminary results and will be the focus of further development.

In conclusion, a practical, chromatography-free synthesis of the potent progesterone antagonist, pyrazole **8** has been developed and used to prepare over 2.5 kg of **8** in an overall yield of 14.5% over five steps.

(9) McCarthy, J. R.; Matthews, D. P.; Paolini, J. P. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. 9, p 446.

(10) The Oxone was added portionwise to a solution of the free base **6** in aqueous methanol, and a thick slurry comprising a mixture of the starting material **6**, product **8**, and Oxone salts was formed. The risk of product entrainment and thus incomplete reaction was considered too high for the process to be practical. Addition of an aqueous Oxone solution to a methanol solution of **6** resulted in immediate precipitation of a slurry, posing the same risks.

(11) Hirt, H.; Haenggi, R.; Reyes, J.; Seeger-Weibel, M.; Gallou, F. *Org. Process Res. Dev.* **2008**, *12*, 111.

Experimental Section

4-[1-(Cyclopropylcarbonyl)-2-oxopropoxy]-2,6-dimethylbenzonitrile (4). A dried, inerted reactor was charged with 1-cyclopropylbutane-1,3-dione **1** (9 kg; 71.3 mol) and dichloromethane (65 kg), and the solution was cooled to 0−5 °C. Trimethylsilyl chloride (7.8 kg; 71.3 mol) was added, followed by a dichloromethane line wash (3 kg), maintaining the temperature between 0−5 °C and the mixture was aged for 30 min at 0−5 °C. A solution of N-chlorosuccinimide (9.34 kg; 69.9 mol) in dichloromethane (298 kg) was then added, carefully controlling the temperature at 0−5 °C (addition took 65 min), followed by a dichloromethane line wash (12 kg). The reaction was stirred for 60 min at this temperature.

The reaction mixture was warmed to 20 °C, hydrochloric acid (2 M, 45 kg) was added, and the mixture was stirred for 5 min. The aqueous phase was discarded, and the dichloromethane solution was then washed with hydrochloric acid (2 M, 45 kg), and water (2 × 45 kg). The reaction mixture was concentrated under vacuum (at 20 °C) to approximately 22 L, acetonitrile (36 kg) was added, and the mixture was concentrated under vacuum to 22 L. This process was repeated to give a solution of 2-chloro-1-cyclopropylbutane-1,3-dione **2** in acetonitrile for further processing.

A solution of 4-hydroxy-2,6-dimethylbenzonitrile **3** (9.9 kg; 67.38 mol) and diisopropylethylamine (8.8 kg; 67.38 mol) in acetonitrile (64 kg) was heated to reflux, and the previously prepared solution of chloride **2** in acetonitrile was added over 50 min, followed by an acetonitrile line wash (2 kg). The resulting mixture was stirred at reflux for 15 h. The reaction mixture was concentrated to ∼25 L, and then the solvent was exchanged to isopropanol through a series of three distill-and-replace cycles, to give a final solution volume of ∼85 L. The solution was cooled to 0 °C and the resulting slurry was aged for 90 min. The solid was isolated by filtration, washed with isopropanol (2 × 17 kg), and dried at 55 °C under vacuum to give the title product **4** (10.88 kg; 60%) as a pale-tan solid. Mp 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 2.51 (s, 6H), 1.98 (s, 3H), 1.87 (m, 1H), 1.15 (m, 2H), 0.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.22, 14.03, 18.96, 21.03, 107.23, 113.70, 117.27, 130.58, 144.91, 161.13, 178.57, 194.44. Anal. Calcd For $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.74; H, 6.32; N, 5.14.

4-[(3-Cyclopropyl-5-methyl-1H-pyrazol-4-yl)oxy]-2,6-dimethylbenzonitrile (5). Hydrazine monohydrate (2.00 kg; 40.1 mol) was added to a solution of ether **4** (10.88 kg; 40.1 mol) in a mixture of denatured ethanol (5% methanol) (54 L) and acetic acid (2.4 kg; 40.1 mol), carefully maintaining the temperature below 30 °C (exothermic addition). The resulting solution was stirred at 20 °C for 1 h. Water (54 L) was then added in one portion, and then further water (54 L) was added over 90 min. The resulting slurry was aged for 4 h and then filtered, washing with water (2 × 25 L), to give the title product **5** (9.95 kg; 93%) as a white solid after drying for 30 h at 55 °C under vacuum. Mp 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.66 (s, 2H), 2.48 (s, 6H), 2.10 (s, 3H), 1.69 (m, 1H), 0.81 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 6.02, 6.33, 9.59, 20.97, 106.69, 113.98, 117.49, 133.19, 144.56, 161.54. Anal. Calcd For $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.89; H, 6.40; N, 15.78.

4-({3-Cyclopropyl-5-methyl-1-[(methylsulfanyl)methyl]-1H-pyrazol-4-yl}oxy)-2,6-dimethylbenzonitrile Hydrogen Sulfate (6a). A solution of pyrazole **5** (6.85 kg; 25.6 mol) in anhydrous 1,2-dimethoxyethane (DME, 18.0 kg) was added to a slurry of potassium *tert*-butoxide (5.75 kg; 51.2 mol) in anhydrous DME (18.0 kg) whilst maintaining the temperature below 20 °C. Once the addition was complete, the slurry was aged at 22 °C for 45 min, and then a solution of chloromethyl methyl sulfide (4.99 kg; 51.2 mol) in anhydrous DME (23.8 kg) was added over 90 min, maintaining the temperature below 30 °C throughout. The reaction was stirred at 20−25 °C for 2 h. Aqueous ammonia (4.5 M; 48 L) was then added, maintaining the temperature between 20−25 °C. After the mixture stirred for 20 min, isopropyl acetate (30 kg) was added, and the phases were separated. The aqueous phase was extracted with a second portion of isopropyl acetate (30 kg) and then disposed to waste. The combined organic extracts were washed successively with water (34 L), sulfuric acid (2 M, 36 L), and water (34 L) and were then concentrated to ∼70 L by distillation; isopropyl acetate (19 kg) was added. and the solution was again concentrated to ∼70 L. The solution was cooled to 50 °C, and concentrated sulfuric acid (2.6 kg; 25.6 mol) was added, followed by an isopropyl acetate line rinse (1.2 kg). The resulting slurry was stirred at 50 °C for 2 h, then cooled to 20 °C over 4 h, and then aged at 20 °C for 6 h before the solid was isolated by filtration, washing with isopropyl acetate (30 L) to give crude product **6a**/**7a** (5.38 kg) as a white solid after drying under vacuum.

The crude product **6a**/**7a** (5.38 kg) was suspended in acetonitrile (16.7 kg), the resulting slurry was stirred at 50 °C for 2 h and then cooled to 20 °C over 2 h. The slurry was then aged at 20 °C for 6 h before the solid was isolated by filtration, washing with acetonitrile (2 × 6.2 kg) to give pure hydrogensulfate salt **6a** as a white solid (4.02 kg; 37%) after drying at 50 °C under vacuum. Mp 157−161 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (br. s. 2H), 6.74 (s, 2H), 5.12 (s, 2H), 2.39 (s, 6H), 2.08 (s, 3H), 2.05 (s, 3H), 1.52 (m, 1H), 0.66 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 4.38, 4.99, 10.37, 14.41, 20.36, 52.02, 106.00, 113.65, 117.01, 132.27, 133.72, 138.73, 144.38, 161.01. Anal. Calcd. For $C_{18}H_{21}N_3OS.H_2SO_4$: C, 50.81; H, 5.45; N, 9.87; S, 15.07. Found: C, 50.75; H, 5.38; N, 9.97; S, 14.94.

4-({3-Cyclopropyl-5-methyl-1-[(methylsulfanyl)methyl]-1H-pyrazol-4-yl}oxy)-2,6-dimethylbenzonitrile (6): prepared by dissolving **6a** in a mixture of water and ethyl acetate, followed by concentration of the organic phase. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 2H), 5.02 (s, 2H), 2.48 (s, 6H), 2.17 (s, 3H), 2.13 (s, 3H), 1.60 (m, 1H), 0.78 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 6.71, 6.76, 8.59, 14.51, 21.00, 52.62, 106.73, 113.98, 117.47, 129.94, 134.09, 144.51, 144.86, 161.46.

4-({5-Cyclopropyl-3-methyl-1-[(methylsulfanyl)methyl]-1H-pyrazol-4-yl}oxy)-2,6-dimethylbenzonitrile Hydrogen Sulfate (7a): prepared from **7** (isolated by chromatography) and concentrated sulfuric acid in isopropyl acetate in analogous fashion to **6a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.98 (br. s, 2H), 6.69 (s, 2H), 5.21 (s, 2H), 2.39 (s, 6H), 2.17 (2, 3H), 1.86

(s, 3H), 1.77 (m, 1H), 0.80 (m, 2H), 0.60 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 4.38, 5.00, 10.37, 14.41, 20.36, 52.02, 106.00, 113.64, 117.01, 132.26, 133.72, 138.72, 144.38, 161.01. Anal. Calcd. For $C_{18}H_{21}N_3OS.H_2SO_4$: C, 50.81; H, 5.45; N, 9.87; S, 15.07. Found: C, 50.82; H, 5.44; N, 9.91; S, 15.10.

4-{[3-Cyclopropyl-1-(mesylmethyl)-5-methyl-1H-pyrazol-4-yl]oxy}−2,6-dimethylbenzonitrile (8). Hydrogensulfate salt **6a** (4.0 kg; 9.4 mol) was suspended in ethyl acetate (40 L), and the mixture was stirred vigorously while a solution of Oxone (5.78 kg; 9.4 mol) in water (29 L) was added. The resulting biphasic mixture was stirred vigorously for 90 min, and then a solution of Oxone (5.78 kg; 9.4 mol) in water (29 L) was added. The mixture was then stirred for a further 2 h, and then a third charge of Oxone (5.78 kg; 9.4 mol) in water (29 L) was added. After a further 6 h stirring, analysis showed incomplete conversion (25% of the intermediate sulfoxide **11** present). A solution of Oxone (5.78 kg; 9.4 mol) in water (29 L) was added, and the mixture was stirred for 6 h. Analysis at this point still showed incomplete conversion (4% sulfoxide **11**), so a further portion of Oxone (5.78 kg; 9.4 mol) in water (29 L) was added, and the resulting mixture was stirred for 14.5 h. The phases were separated, and the aqueous phase was extracted with ethyl acetate (36 kg). The combined organic phase was washed with water (40 L) and filtered through a 1.2 μm filter, and then the solution was concentrated to ~20 L by distillation. Isopropanol (31.4 kg) was added, and the solution was again concentrated to ~20 L by distillation. Isopropanol (31.4 kg) was added, and the solution was concentrated to 34 L by distillation. The solution was then cooled to 20 °C over 2 h, and the resulting slurry was aged at 20 °C for 6 h before the solid was isolated by filtration, washing with isopropanol (2 × 15.7 kg). The solid was then dried at 55 °C under vacuum for 8 h to give the product **8** (2.54 kg; 75%) as a white solid. Mp 163−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 2H), 5.12 (s, 2H), 2.96 (s, 3H), 2.48 (s, 6H), 2.17 (s, 3H), 1.62 (m, 1H), 0.80 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 6.69, 7.40, 8.78, 21.00, 40.04, 67.67, 107.08, 113.97, 117.35, 133.10, 134.55, 144.65, 148.46, 161.01. Anal. Calcd For $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.22; H, 5.87; N, 11.78; S, 9.10.

4-{[5-Cyclopropyl-1-(mesylmethyl)-3-methyl-1H-pyrazol-4-yl]oxy}-2,6-dimethylbenzonitrile (12). Prepared in an analogous fashion to **8** by oxidation of **7a** with Oxone in a water/ethyl acetate mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (s, 2H), 5.32 (s, 2H), 3.08 (s, 3H), 2.49 (s, 6H), 2.04 (s, 3H), 1.77 (m, 1H), 0.88 (m, 2H), 0.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.18, 5.18, 10.68, 21.02, 40.21, 67.49, 107.10, 113.85, 117.33, 134.39, 137.13, 143.32, 144.68, 160.97.

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