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TECHNICAL NOTE

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Work-Up Optimization en Route to an Improved Process To Prepare a Progesterone Receptor Antagonist

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Supporting Information

ABSTRACT: When the process to prepare nonsteroidal progesterone receptor antagonist **5** was scaled up, significant problems were encountered, and as a result lower than expected yields were obtained. In particular, the alkylation of pyrazole **2** with chloromethyl methyl sulfide failed to reach completion, and partial degradation of the product occurred during the work-up, resulting in a modest yield of alkylated pyrazole **3a**. Further investigation has revealed the root cause of this problem, and an improved, robust process to **5** has been developed.

INTRODUCTION

We recently disclosed our initial synthetic route to the nonsteroidal progesterone receptor antagonist, 4-{[3-cyclopropyl-1-(mesylmethyl)-5-methyl-1*H*-pyrazol-4-yl]oxy}-2,6-dimethylbenzonitrile, **5**, and the application of this process to deliver ∼2.5 kg of **5** for initial clinical investigations (Scheme 1).[1] As this project advanced through development, additional supplies were required, and this route was supplied to an external vendor in order to prepare 15 kg of **5**. While some minor difficulties were encountered with the early steps to prepare pyrazole **2**, in particular the chlorination/displacement sequence (Scheme 1, steps a, b), these were readily resolved, and these steps performed as expected, delivering a 50% yield, comparable to that seen previously (56%).

The final oxidation step also proceeded as expected (Scheme 1, step h), apart from requiring an additional charge of Oxone. However, the key alkylation/purification sequence (Scheme 1, steps d−g) did not work as expected, with a disappointing 27% yield of the desired pyrazole hydrogensulfate salt **3a** being isolated (previously this was 37%). The main reason for this yield loss was incomplete alkylation of pyrazole **2**, with ∼15% remaining in the reaction mixture despite extended reaction times. As a result, the final two steps afforded only a 21% yield of **5** from pyrazole **2**, significantly lower than the 28% obtained in the first manufacturing campaign. While sufficient material was delivered to progress the project (around 11 kg of **5**), it had highlighted a scale-up issue that would need to be addressed prior to any future campaigns.

RESULTS AND DISCUSSION

In the initial process,[1] addition of chloromethyl methyl sulfide to a mixture of the pyrazole **2** and base was carried out over 90 min, and this had worked well on ∼6.5 kg **2**; however, when scaling up to ∼35 kg, the addition time had not been re-evaluated. On the basis of the observed result, it was apparent that slowing down the chloromethyl methyl sulfide addition rate further was required as the process scale increases. Due to the heterogeneous nature of the reaction mixture, all attempts at in situ monitoring of the reaction in order to get accurate kinetic information were not successful; therefore, the decision was made to simply add the chloromethyl methyl sulfide solution as slowly as possible (based on equipment limitations) for future campaigns.

In a subsequent in-house campaign on approximately the same scale, extending the addition time to 180 min resolved this problem, with the completion of reaction HPLC analysis showing 1.5% **2** remaining. However, the isolated product **3a** was found to contain ∼20% **2a**, and as a result, when this batch was processed through the final step, the isolated **5** failed specifications (1% **2** present) and required an additional recrystallization from IPA to deliver acceptable material, thus reducing the overall yield (33% from **2**). While this overall yield was a significant improvement on previous campaigns, the lack of robustness needed to be addressed, as the additional recrystallization increased the number of processing steps, as well as resulting in a yield loss.

The unexpectedly high level of **2a** found in the isolated **3a** is due to partial degradation of the mixture of **3** and **4** during the work-up and isolation process. This instability had been observed in both lab batches, and the previous in-house campaign.[1] However, in these cases the level of the unsubstituted pyrazole **2a** in the first isolated solid was around 10%, in addition to ∼15% of the unwanted regioisomer **4a**. The subsequent acetonitrile reslurry had efficiently purged both **2a** and **4a**, and the final API **5** had met specifications. In this latter larger-scale batch, however, the level of **2a** in the crude intermediate was 13%, and this had not purged in the acetonitrile reslurry (due to the purge of **4a**, the relative amount of **2a** actually increased). Consequently, the isolated **3a** contained ∼20% **2a**, resulting in an out-of-specification level of **2** in the isolated API **5**.

In order to identify the root cause for the formation of **2**, the work-up process was examined in more detail. The process consists of three distinct stages, as follows:

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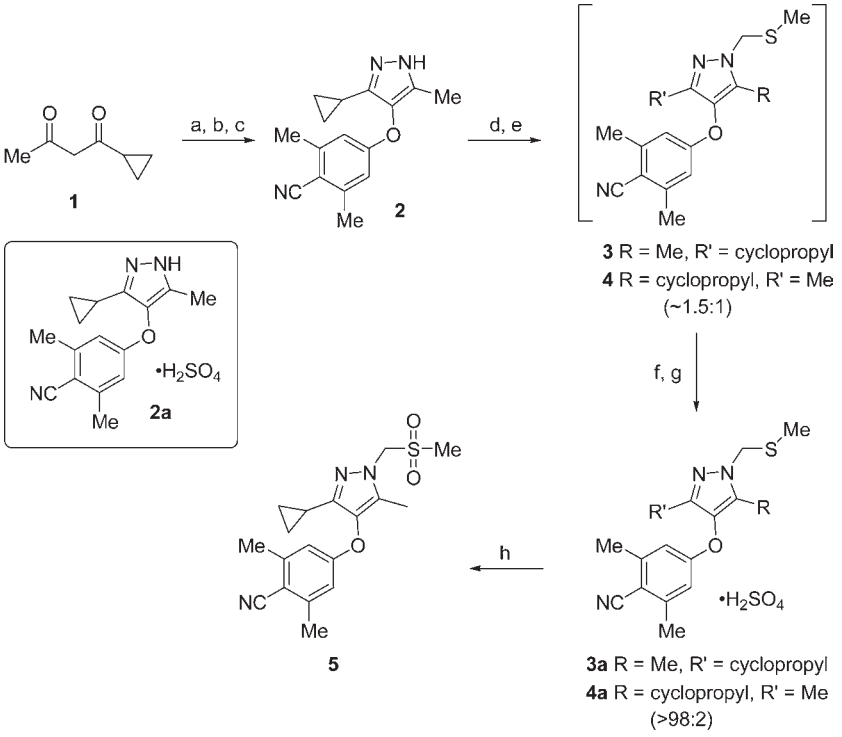
Scheme 1. [a] **Synthetic route to 5**



a Reagents and Conditions: (a) NCS, TMSCl, DCM, 0−5 °C; (b) 4-hydroxy-2,6-dimethylbenzonitrile, iPr_2NEt, MeCN, reflux, then iPrOH; (c) $H_2NNH_2 \cdot H_2O$, AcOH, EtOH, 25 °C, then H_2O, 56% over three steps; (d) KOtBu, 1,2-DME 0 °C to RT; (e) $ClCH_2SMe$, 1,2-DME (slow addition); (f) H_2SO_4, iPrOAc; (g) MeCN reslurry, 37% overall. (h) (i) Oxone, EtOAc, water; (ii) IPA recryst, 75%.

1. The reaction is quenched with ammonia to destroy any residual chloromethyl methylsulfide, followed by extraction with isopropyl acetate. The isopropyl acetate solution is washed with water and dilute acid and is then partially concentrated by distillation at atmospheric pressure to remove residual water.
2. The isopropyl acetate solution is cooled to 50 °C and conc. sulfuric acid is added. The resulting slurry is stirred at 50 °C for 2 h, cooled to 20 °C over 4 h, and aged at 20 °C for 6 h, affording crude product **3a** (containing ~10% **2a**, ~15% **4a**, and other minor impurities) after isolation by filtration.
3. The crude product **3a** is slurried at 50 °C in acetonitrile for 2 h, cooled to 20 °C, and aged for 6 h, affording pure product **3a** containing NMT 1% of **2a** and **4a**, after isolation.

Analysis of the reaction mixture at each stage showed that no degradation occurs during either the work-up (stage 1) or the acetonitrile reslurry (stage 3). During the crude salt formation (stage 2), the level of pyrazole **2** increases, indicating instability of **3** and **4** under these conditions.

Methylthiomethyl ethers (MTM) are generally used as protecting group for alcohols, and in this role are reported to be stable under acidic conditions.[2] Given that in this case the MTM group is attached to a pyrazole ring (rather than an alcohol), it is perhaps not surprising that some instability under acidic conditions is observed as the protonated pyrazole would be expected to be a good leaving group. While this instability is clearly acid-related, a number of potential contributing factors were identified. Therefore, a small statistical study was conducted in order to examine the effects of temperature, sulfuric acid charge, water content and time of addition (of sulfuric acid) on the level of **2** (or **2a**) present in the reaction mixture prior to isolation. As some purge of **2** (or **2a**) is likely to occur during the crystallization process, all analysis was done on crude reaction mixtures with care taken to sample the slurry as representatively as possible.

The experimental design was based on a Taguchi L8 array with four factors at two levels each and is equivalent to a conventional 2^{4-1} fractional factorial. The column assignment was designed to minimize the aliasing between main effects and interactions; two centre point runs were also included (reactions 0 and 9). The experimental design is shown in Table 1 below. Data were collected at three time points, immediately after addition of acid (T 0), after 1.5 h (T 1.5) and after stirring overnight (16 h; T O/N), these results are also shown in Table 1. In all cases, the amount of **2** was measured, however for the statistical analyses, the level present in the ingoing material (Start) was subtracted to measure the increase.

From a review of these data, it was evident that temperature is by far the dominant factor in degrading the products **3** and **4** back to the starting material **2**, as shown in Figure 1. The statistical significance was confirmed with half-Normal and ANOVA tests. The dependence on temperature is clearly shown in Figure 2, where the rate of degradation is significantly higher at 70 °C, but even at 30 °C fairly substantial levels are formed (>10% after 1.5 h). Each point on the graph is the average of the trials with the chosen temperature and has a balanced combination of the other parameter settings to remove potential bias. A more detailed statistical analysis is provided in the Supporting Information.

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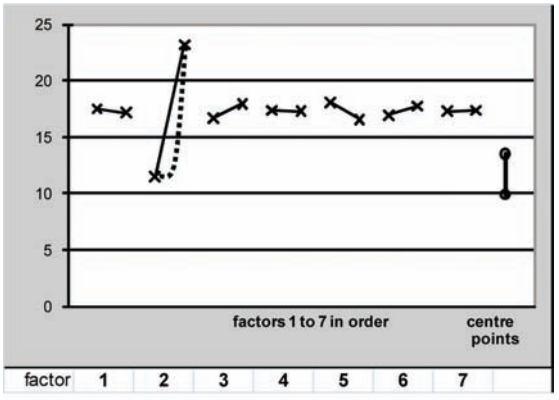
Table 1. Design of the experiment and results

					amount of **2** present (%)			
rxn	H_2SO4 (equiv)	temp (°C)	water (%)	addition time (min)	start	*T* 0	*T* 1.5	*T* O/N
0	1.0	50	0.20	15	3.5	7.6	15.7	17
1	0.8	30	0.05	5	3.1	5.4	9.1	14.5
2	0.8	30	0.40	25	3.4	6.8	11.6	14.1
3	0.8	70	0.05	25	3.6	18.2	27.2	28.8
4	0.8	70	0.40	5	3.4	12	24.9	26.1
5	1.2	30	0.05	25	3.7	8.4	13.8	14.6
6	1.2	30	0.40	5	3.3	7	12.8	16.3
7	1.2	70	0.05	5	3.7	18.7	23	25.7
8	1.2	70	0.40	25	3.1	14	24.3	25.8
9	1.0	50	0.20	15	4.2	7.9	14.9	14.1



Physical values of the levels

factor	name	level 1	level 2
1	H2SO4	0.8eq	1.2eq
2	Temperature	30°C	70°C
3	ht wa		
4	Water	0.045%	0.4%
5	hw ta		
6	tw ha		
7	Addition time	5min	25min

Figure 1. Effects of factors on impurity generation after overnight stir.

On the basis of these results, the process used to generate the pyrazole salt **3a** was modified as follows: the temperature was reduced to 20 °C, and the age time was reduced to 3 h at 20 °C. Laboratory experiments showed that by using this modified process the level of the unwanted regioisomer **4a** present in the first isolated solid increased (~20% instead of ~15%) and the level of degradation was reduced slightly with 5−8% **2a** present (in the original process this was around 10%). In addition, the isolated yields were generally higher, possibly as a result of less degradation. However, the acetonitrile reslurry efficiently removed both **2a** and **4a** when present at these levels, and the isolated **3a** contained around 1% of each (a level that is known to purge in the final step[1]). This modified process was then transferred to the plant. Two batches were run using ~42 kg input **2**, and both delivered a consistent 60% yield of crude pyrazole salt **3a** that contained 8% **2a** and 19% **4a**. These two batches were combined

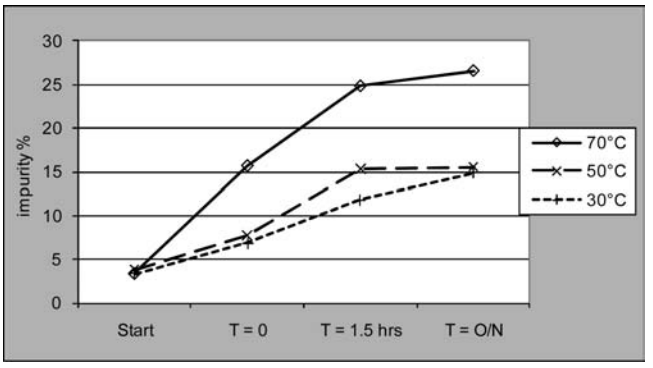


Figure 2. Effects of time and temperature.

for a single acetonitrile reslurry that successfully purged both impurities to NMT 1%, affording 55.85 kg of pure **3a** (69% yield). Over the entire process the overall yield was an acceptable 41%.

Due to the improved quality of the input, pyrazole salt **3a**, 41.4 kg **5** was obtained in an excellent 88% yield from the final step (instead of the usual 75%). Overall, as a result of the yield improvements obtained in the alkylation step and work-up, the modified process delivered **5** in a significantly improved 36% yield from **2**.

EXPERIMENTAL SECTION

4-({3-Cyclopropyl-5-methyl-1-[(methylsulfanyl)methyl]-1*H*-pyrazol-4-yl}oxy)-2,6-dimethylbenzonitrile hydrogen sulfate (3a). A solution of pyrazole **2** (42.4 kg; 158.7 mol) in anhydrous 1,2-dimethoxyethane (DME, 110.4 kg) was added to a slurry of potassium *tert*-butoxide (35.6 kg; 317.4 mol) in anhydrous DME (92.0 kg) whilst maintaining the temperature below 20 °C. Once the addition was complete, the line was washed with DME (36.8 kg). The resulting slurry was aged at 22 °C for 45 min, and then a solution of chloromethyl methyl sulfide (30.65 kg; 317.4 mol) in anhydrous DME (147.1 kg) was added at a constant rate of 30−35 L/h (addition took around 4.5 h), maintaining the temperature below 30 °C throughout. The lines were washed with DME (9.7 kg). The reaction was stirred at 20−25 °C for 4.5 h, then a solution of ammonia (35 wt % in water; 74 kg) in water (245 L) was added, maintaining the temperature between 20 and 25 °C. After stirring for 20 min, isopropyl acetate (185 kg) was added, and the phases were separated. The aqueous phase was extracted with a second portion of isopropyl acetate (185 kg) and then disposed to waste. The combined organic extracts were washed successively with water (212 L), sulfuric acid (2 M, 212 L), and water (212 L) and were then concentrated to ~420 L by distillation; isopropyl acetate (111 kg) was added, and the solution was again concentrated to ~420 L. The solution was cooled to 20 °C, and concentrated sulfuric acid (15.6 kg; 158.7 mol) was added over 20 min, keeping the temperature below 25 °C, followed by an isopropyl acetate (7.2 kg) line wash. The resulting slurry was stirred at 20 °C for 3 h, then the solid was isolated by filtration, washing with isopropyl acetate (185.0 kg) to give crude product **3a**/**4a** (39.82 kg) as a white solid after drying under vacuum.

The crude product was then combined with a similar sized batch to give **3a**/**4a** (81.37 kg), which was suspended in acetonitrile (255.8 kg). The resulting slurry was stirred at 50 °C for 3 h and then cooled to 20 °C over 2 h. The slurry was then aged at 20 °C for 14 h before the solid was isolated by filtration, washing

with acetonitrile (2 × 95.9 kg) to give acceptable quality hydrogensulfate salt **3a** as a white solid (55.85 kg; 41%) after drying at 50 °C under vacuum. Analytical data matched those previously published.[1]

■ ASSOCIATED CONTENT

Supporting Information. Full details of the statistical analysis conducted. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ADDITIONAL NOTE

†Address questions regarding the statistical analysis to this author. E-mail: george@grb.co.uk.

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