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Development of Scalable Processes for the Preparation of N-Methyl-3-Bromo-5-Methyl Pyrazole

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*To whom correspondence should be addressed. E-mail: richard.fox@bms.com
1. NC=Me → Me 3 steps → Me

   - Sandmeyer approach
   - 3 HCl salt sublimation
   - 19-28% overall yield

2. Br + HX → 3 HCl, X = Cl

3. 3 TfOH, X = OTf

4. MeO2C=Me 3 steps

   - Sandmeyer avoided
   - Robust 3 TfOH isolation
   - 38-42% overall yield
Abstract

The development and optimization of two scalable routes to N-methyl-3-bromo-5-methyl pyrazole is described. The initial Sandmeyer route entailed a 3-step sequence from crotonitrile and methyl hydrazine, proceeding through the 3-amino pyrazole intermediate. Due to the GTI liability of the 3-amino pyrazole intermediate, a tedious steam-distillation, and <30% overall yield, we developed a second-generation Sandmeyer-free approach from methyl crotonate and methyl hydrazine which leveraged a condensation, bromination, oxidation sequence. Process development led to the improved preparation of N-methyl-3-bromo-5-methyl pyrazole with increased efficiency and overall yield. The isolation, handling and storage of the final product was greatly improved through the generation of the triflic acid salt, and salt form studies are also discussed.

Keywords: N-methyl-3-bromo-5-methyl pyrazole, bromopyrazole, Sandmeyer halogenation, regioselective methyl hydrazine addition, dihydropyrazole oxidation
**Introduction**

Halogenated pyrazoles represent an important class of heterocycles due to their presence in biologically active compounds,\(^1\) as well as their synthetic utility as starting materials for further functionalization.\(^2\) A variety of methods have been reported for the formation of 3, 4, and 5-halogenated pyrazoles, with 3-halopyrazoles most often prepared via: (1) direct electrophilic bromination when the C(4) substituent is not hydrogen, (2) dehydroxyhalogenation of 3-hydroxypyrazoles, (3) bromination of N-oxides,\(^3\) (4) Hunsdiecker decarboxylation/halogenation, (5) N-1 alkylation, (6) cycloaddition methodologies, (7) Pd-catalyzed coupling via C(5) nonaflates and (8) diazoniation of 3-aminopyrazoles (i.e., Sandmeyer) (Figure 1).\(^4\) While these approaches have been successful for a variety of targets, the synthesis of N-methyl-3-bromo-5-methyl pyrazole (i.e., R\(_1\) = R\(_2\) = Me and R\(_3\) = H, Figure 1) had not been reported.

**Figure 1.** Known Approaches to 3-Bromopyrazoles
Herein we describe our efforts towards developing two scalable processes for the preparation of N-methyl-3-bromo-5-methyl pyrazole (3) (Scheme 1). The initial Sandmeyer route entailed a 3-step telescoped process from crotonitrile and methyl hydrazine and proceeded through 3-aminopyrazole 2. An improved second-generation approach was then developed from methyl crotonate and methyl hydrazine which leveraged a sequence consisting of condensation, followed by bromination and oxidation. Salt form studies for N-methyl-3-bromo-5-methyl pyrazole (3) are also presented.

Scheme 1. Routes to N-methyl-3-bromo-5-methyl pyrazole (3)

Results and Discussion

For a recent program we needed to prepare multi kilogram amounts of N-methyl-3-bromo-5-methyl pyrazole (3). We initially investigated the preparation of 3 utilizing a variety of known methodologies for 3-bromopyrazoles, but these approaches were unsuccessful. For example, bromination of 6 is known to lead to bromide 7,5 6 was resistant to oxidation,6 and N-methylation of 14 led to a mixture of regioisomers. Likewise, C(3) bromination of 9 led to undesired decarboxylation/bromination to afford 11,6 while attempted Hunsdiecker decarboxylation/halogenation of 12 led to bromide 13. C(3) bromination of 9 led to undesired decarboxylation/bromination to afford 11,7 while 12 did not undergo the desired decarboxylation, but instead led to bromide 13 (Figure 2).
Figure 2. Unsuccessful Approaches to 3

Based on our previous report\textsuperscript{8} that described both the unsuccessful conversion of hydroxypyrazole 15 to either 3 or the chloro derivative 16, along with the preparation of iodopyrazole 17 from known aminopyrazole 2,\textsuperscript{9} we selected a Sandmeyer strategy for our initial route to 3 (Scheme 2).

Scheme 2. Previous Attempts to 3 and Sandmeyer Route to 17

The first-generation synthesis of 3 began with bromination of commercially available crotononitrile (1) (Table 1). During our process development, we found that the two most important variables for the bromination were the addition of catalytic acid and addition order. Specifically, while the reaction of 1 with bromine in DCM was slow, addition of 0.05 equiv of HBr dramatically increased
the reaction rate. Reaction calorimetry also indicated that addition of HBr to the mixture of 1 and bromine in DCM, followed by heating to 30°C, had both an adiabatic temperature rise of 84.3°C, and a sharp spike in the heat liberation rate to 88 W/kg shortly after reaching 30 °C. On the other hand, controlled addition of 1 in DCM to a solution of bromine and HBr in DCM reduced the peak heat liberation rate to 57 W/kg, with 98% of heat liberation occurring over the course of the addition. Control during this addition was important as a strong exotherm could lead to loss of bromine and significant unreacted 1. The optimized reaction conditions entailed addition of a solution of 1 in 2 L/kg DCM over 4 h to a mixture of 1.0 equiv Br₂ and 5 mole% 33% HBr in acetic acid in 13 L/kg DCM to maintain the internal temperature <35 °C. Following aqueous workup, concentration of the DCM solution under vacuum led to 18 as a neat oil. This procedure was successfully executed on 3 x 145 kg batches to afford 18 in 84% average corrected yield with 93.9 liquid chromatography area percent (LCAP), 2.5-2.6 LCAP unreacted 1, and 91-95 wt%.

Table 1. Preparation of 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>MeNH₂ source (equiv)</th>
<th>Base (equiv)</th>
<th>Solvent (L/kg)</th>
<th>Isolated 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄ salt (3.0)</td>
<td>K₂CO₃ (3.0)</td>
<td>Water (30)</td>
<td>88-93 LCAP, 59-73 wt% 2.1-5.0 LCAP 19 36-47% yield from 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MeOH (8.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H₂SO₄ salt (1.25)</td>
<td>10 N NaOH (5.2)</td>
<td>Water (4.2)</td>
<td>93-95 LCAP, 78-86 wt% &lt;1 LCAP 19 77-84% yield from 18</td>
</tr>
<tr>
<td>3</td>
<td>freebase (1.25)</td>
<td>10 N NaOH (8.0)</td>
<td>Water (4.2)</td>
<td>97 LCAP, 98 wt% &lt;1 LCAP 19 83% yield from 18</td>
</tr>
</tbody>
</table>
With respect to the conversion of 18 to 2, the initial conditions utilized 3.0 equivalents of both MeNHNH₂•H₂SO₄ and K₂CO₃ in water/MeOH and led to 2 in only modest yield and potency, along with up to 5.0 LCAP of undesired isomer 19 (Table 1, entry 1). Fortunately we found that highly basic reaction conditions (pH >13) minimized the formation of 19, and the conditions in entry 2 were successfully executed on 250-350 kg scale to afford 2 in 77-84% corrected yield with 93-95 LCAP (<1 LCAP 19) and 78-86 wt%. While these conditions were scalable, the initial neutralization of the sulfate salt with sodium hydroxide was highly exothermic. For this reason, commercially available methylhydrazine freebase was also examined, and the modified conditions in entry 3 afforded 2 in 83% yield with 97 LCAP and 98 wt% on 500 g scale.

As 2 was found to be an AMES positive genotoxic intermediate (GTI), it was also desirable to develop a workup protocol that would eliminate the isolation of neat 2. Towards this end, following the addition of 1 L/kg toluene at the end of the reaction, the layers could be split, and the resulting product-rich aqueous layer washed with 6 x 1.5 L/kg DCM. The combined DCM layers could then be solvent swapped into 5 L/kg CH₃CN, assayed for potency, and telescoped into the Sandmeyer chemistry.¹¹

The final optimized process for the conversion of 2 to 3•HCl is shown in Scheme 3. Some of the key process development knowledge entailed: (1) Cu(I)Br¹² was critical, as use of Cu(II) bromide led to an undesired regioisomer; (2) conducting the reaction with 30% water in acetonitrile, versus 100% CH₃CN, increased the end of reaction purity from ~50 to 80 LCAP; (3) slow addition (>1 h) of isoamyl nitrite was required to minimize the rate of N₂-offgasing; and (4) the concentrated reaction mixture was found to be unstable in the presence of unreacted isoamyl nitrite and copper salts.¹³ To address this last observation, 10 volumes of water were charged at the end of reaction, and the stream was filtered through celite to remove copper salts prior to initiating a constant-volume steam distillation.¹⁴
Scheme 3. Preparation of 3•HCl from 2

The constant-volume steam-distillation was conducted at atmospheric pressure, charging a total of 40 L/kg water. The distillate collected between 80-100 °C afforded 3 with ~90 LCAP, along with ~10 LCAP des-bromide 6. While this distillation was an effective clean-up strategy, it required 4 days of continuous processing on 100 kg scale. Fortunately, we confirmed prior to the scale-up that no safety or quality liabilities were observed during the analysis of both batch and distillate samples taken over the course of 10 days.

To complete the isolation, the aqueous distillate of 3 was extracted with MTBE/1 N HCl. Using this protocol, des-bromide 6 was selectively protonated and extracted into aqueous layer. The organic phase was then dried and concentrated to 5 L/kg. Reduction of the water content of the organic stream was critical to control losses to the mother liquor during the crystallization. Typical yields at this stage were 35-45%, with the main source of process variability resulting from batch-to-batch differences in the steam distillation of 3. Controlled addition of 2 equiv of 5-6 N HCl in isopropanol then furnished 3•HCl. Using this process, 196 kg 3•HCl was prepared in 26-39% yield with excellent purity [99.9 LCAP, < 4ppm 2 (GTI)].

Concurrent with the efforts associated with the development and scale-up of the Sandmeyer route, we identified both shipping and stability liabilities of 3•HCl. Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA) and materials compatibility testing with Armorflex (AF110) bags confirmed that 3•HCl began to sublime at temperatures as low as 40 °C. Additionally, 3•HCl was observed
to deliquesce upon exposure to elevated humidity, and Moisture Sorption Analysis indicated complete sublimation by 85% relative humidity. Thus, there was a risk of significant mass loss during shipment and storage of kilogram quantities of $3\cdot\text{HCl}$. As a stop-gap measure, the material generated during the initial scale-up was shipped and stored cold. However, to reduce or eliminate these shipping and storage concerns in future batches, alternative salt forms of $3$ were investigated.

As shown in Table 2, a broad screen supported that use of acids weaker than HCl led to either no crystallization or highly hygroscopic solids. The theoretical pK$_a$ of the conjugate acid of $3$ was estimated to be ~0.5,$^{17}$ indicating that bromopyrazole $3$ was significantly less basic than des-Br pyrazole $6$, which had an experimental pK$_a$ value of 2.5.$^{18}$ This observation suggested that acids stronger than HCl might be required to protonate $3$. $^{19}$ To our delight, the triflate salt of $3$ was a highly crystalline solid with no sublimation liabilities and only mild hygroscopic character that was easily addressed by the addition of desiccant during shipment and storage.

Table 2: Acid Salt Screen of $3$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Acid pK$_a$</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tartaric acid</td>
<td>4</td>
<td>no solids</td>
</tr>
<tr>
<td>2</td>
<td>Succinic acid</td>
<td>4</td>
<td>no solids</td>
</tr>
<tr>
<td>3</td>
<td>4-NO$_2$ benzoic acid</td>
<td>3.4</td>
<td>no solids</td>
</tr>
<tr>
<td>4</td>
<td>Fumaric acid</td>
<td>3.0</td>
<td>no solids</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>0.25</td>
<td>no solids</td>
</tr>
<tr>
<td>6</td>
<td>CSA</td>
<td>-2.5</td>
<td>solids deliquesce</td>
</tr>
<tr>
<td>7</td>
<td>MSA</td>
<td>-2.6</td>
<td>solids deliquesce</td>
</tr>
<tr>
<td>8</td>
<td>H$_2$SO$_4$</td>
<td>-3.0</td>
<td>solids deliquesce</td>
</tr>
<tr>
<td>9</td>
<td>benzenesulfonic acid</td>
<td>-3.0</td>
<td>solids deliquesce</td>
</tr>
<tr>
<td>10</td>
<td>HCl</td>
<td>-8.0</td>
<td>sublimes at 40 °C</td>
</tr>
</tbody>
</table>
Having identified the triflate salt form of 3, we turned our attention to the development of an alternative route to 3•TfOH that would eliminate both the GTI liabilities associated with 2, and tedious steam-distillation, as well as improve the overall yield. Towards this end, we were attracted to a synthetic strategy in which the 3-bromo moiety would be introduced at an earlier stage in the process, followed by a final oxidation step of the corresponding dihydropyrazole intermediate to furnish 3.\(^{20}\)

Our efforts towards a second-generation route to N-methyl-3-bromo-5-methyl pyrazole (3) began with the condensation of methyl hydrazine and methyl crotonate (4). While this transformation had not been reported,\(^{21}\) literature precedent supported that 20 would be the favored regioisomer.\(^{22}\) As shown in Table 3, while our initial studies (entries 1-4) demonstrated that the use of water or methanol led to the highest (i.e., 8-15:1) in-process (IP) regioselectivity, the high solubility (i.e., >100 mg/mL) of 20•HBr, which was the ideal salt form to minimize halogen exchange in the subsequent bromination, in these solvents made a direct drop isolation challenging. On the other hand, while the low (i.e., <5 mg/mL) solubility of 20•HBr in IPA was attractive with respect to isolation, both the rate and regioselectivity for the condensation were not optimal. Entries 5 and 6 demonstrated that running at higher concentrations and adding 5 mole% NaOH increased both the reaction rate and regioselectivity; variable dissolution of NaOH in IPA was the presumed cause of the selectivity range from 7-11:1. Due to the increased solubility of KOH in IPA, our optimized process utilized 5 mole% KOH in 2.3 L/kg IPA at ambient temperature, and reproducibly led to a 13:1 in-process ratio of 20:21 (entry 7).\(^{23}\) Following seeding with 20•HBr, addition of 1.1 equiv of HBr in IPA (prepared from 1.1 equiv acetyl bromide in 9.3 L/kg IPA) led to 20•HBr in 90% isolated yield with >99.5 LCAP purity and 99 wt% on 40 g scale. Pleasingly, this chemistry was successfully conducted on 72 kg scale to produce 20•HBr with >99 LCAP in 85% yield.
Table 3. Preparation of 20•HBr

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (L/kg)a</th>
<th>Additive</th>
<th>Conversion after 4 h b</th>
<th>IP ratio 20:21b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat</td>
<td>none</td>
<td>&gt;95%</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>water (10)</td>
<td>none</td>
<td>&gt;95%</td>
<td>15:1</td>
</tr>
<tr>
<td>3</td>
<td>MeOH (10)</td>
<td>none</td>
<td>&gt;95%</td>
<td>8:1</td>
</tr>
<tr>
<td>4</td>
<td>IPA (10)</td>
<td>none</td>
<td>85%</td>
<td>4:1</td>
</tr>
<tr>
<td>5</td>
<td>IPA (2.3)</td>
<td>none</td>
<td>&gt;95%</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>IPA (2.3)</td>
<td>0.05 eq NaOH</td>
<td>&gt;95%</td>
<td>7-11:1</td>
</tr>
<tr>
<td>7</td>
<td>IPA (2.3)</td>
<td>0.05 eq KOH</td>
<td>&gt;95%</td>
<td>13:1</td>
</tr>
</tbody>
</table>
```

a L/kg based on methyl hydrazine. b Determined by HPLC.

Turning to the conversion of 20•HBr to 5, a brief screen of conditions supported: (1) POBr3 was uniquely effective for this transformation, (2) reaction rates were comparable in DCM and CH3CN, (3) base was required, and (4) while Et3N, DIPEA and 2,6-lutidine were all acceptable, K2CO3 led to low conversion.24 Due to the anticipated need for an aqueous workup to both quench the excess POBr3 and remove the organic base, the combination of DCM and Et3N was selected for further development.

As summarized in Table 4, further optimization led to two key findings: (1) 0.9 equiv Et3N was optimal (entries 1-4), and (2) while catalytic DMF, N-methyl morpholine (NMM) and DABCO25 were not beneficial (entries 5-7), addition of 0.3 equiv Et4NBr significantly increased the reaction rate (entry 8). This rate enhancement correlated well with FTIR data that supported 20•HBr rapidly converted to 22 upon addition of POBr3, and conversion of 22 to 5 was rate-determining.26 Final optimization of concentration
and temperature decreased the time needed to reach >95% conversion from approximately 20 h to 5 h (entry 9).

**Table 4. Optimizing Conversion of 20·HBr to 5**

<table>
<thead>
<tr>
<th>Entry</th>
<th>L/kg DCM</th>
<th>Et₃N equiv</th>
<th>Additive (equiv)</th>
<th>Temp (°C)</th>
<th>LCAP 5¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.7</td>
<td>none</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.9</td>
<td>none</td>
<td>20</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1.1</td>
<td>none</td>
<td>20</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>2.2</td>
<td>none</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.9</td>
<td>DMF (0.1)</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>0.9</td>
<td>NMM (0.1)</td>
<td>20</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>0.9</td>
<td>DABCO (0.1)</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>0.9</td>
<td>Et₄NBr (0.3)</td>
<td>20</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>0.9</td>
<td>Et₄NBr (0.3)</td>
<td>30</td>
<td>95</td>
</tr>
</tbody>
</table>

¹ After 7 h at 20 °C for entries 1-8 and 5 h at 30 °C for entry 9

For the aqueous workup, initial experimentation revealed the partitioning of 5 into aqueous solution was highly dependent on pH, with ~15% yield loss observed at pH 1.5, but <3% yield loss at pH >4.5. As shown in Table 5, in order to remove both the residual Et₃N and Et₄NBr prior to the subsequent oxidation, our initial workup entailed addition of aqueous KOH to the reaction mixture to obtain a final pH of 4-5 (entry 1). Unfortunately, this led to a challenging emulsion. Based on the higher water solubility of NaH₂PO₄ vs KH₂PO₄, presumably the major phosphate salt present at pH 4-5 after quenching the excess POBr₃, we replaced KOH with NaOH. This led to a clean phase split, removal of both the Et₃N and Et₄NBr, and 5 in 74% in-process yield (entry 2). Switching to an inverse aqueous NaOH quench not only led to a more controlled exotherm, but further improved the IP yield, presumably due to maintaining the...
pH >4 throughout the quench (entry 3). Overall, the final workup protocol involved addition of the bromination reaction mixture into 4.5 equiv NaOH in 19 L/kg water at 0 °C, followed by warming to 20 °C, and washing the resulting DCM layer sequentially with 5 L/kg 0.1 M Na₂HPO₄ and 5 L/kg water. Under these conditions, 5 was isolated in 93% solution yield with excellent purity on 30 g scale. This chemistry proved extremely robust, leading to 5 in 97% solution yield on 73 kg scale.

**Table 5. Investigating POBr₃ Workup Protocol**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quench solution</th>
<th>Addition mode</th>
<th>Final pH</th>
<th>Emulsion observed</th>
<th>Et₃N in org layer⁴</th>
<th>Et₄NBr in org layer⁴</th>
<th>IP yield⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>aq KOH</td>
<td>normal</td>
<td>4-5</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>ND⁶</td>
</tr>
<tr>
<td>2</td>
<td>aq NaOH</td>
<td>normal</td>
<td>4-5</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>aq NaOH</td>
<td>inverse</td>
<td>4-5</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>93%</td>
</tr>
</tbody>
</table>

⁴ Determined by ¹H NMR. ⁵ Determined by ¹H NMR of final 5/DCM solution using 1,2-dichloroethane as internal standard. ⁶ ND = not determined.

Continuing with the proposed telescope, an extensive screen of oxidants supported that NaOCl, t-BuOOH/VO(acac)₂ and MnO₂ were most effective in converting 5 to 3.²⁴ Due to the scale-up challenges of MnO₂, and minimal purity profile differences between NaOCl and t-BuOOH/VO(acac)₂,²⁹ NaOCl was selected for further optimization. Our initial trials were conducted by adding 1 equiv of aqueous NaOCl to a biphasic solution of 5 in DCM and 1 equiv K₃PO₄ in 5 L/kg water at 0-5 °C. Unexpectedly, we observed a significant induction period under these conditions (Figure 3). Based on the well-precedented impact of bromide additives in TEMPO/bleach oxidations,³⁰ we next charged 0.1 equiv of KBr at the start of the reaction. With the addition of KBr, we observed the expected near addition controlled kinetics. Taken together, these results supported that HOBr was the active oxidant, and the induction period observed in the absence of KBr was likely due to the time needed to induce some hydrolysis of 5 to release bromide into the reaction mixture.
Further optimization led to our final oxidation conditions which entailed the slow addition of 1.75 equiv of aqueous NaOCl to a biphasic mixture of 5 in DCM and 2 equiv K₃PO₄ and 0.5 equiv KBr in 2 L/kg water at 0-5 °C (Table 6). The use of 2 equiv K₃PO₄ was critical to maintain the pH >12 and minimize formation of dibromide 24. For example, subjecting 3 to the reaction conditions with pH 12 buffer led to <2 LCAP 24 after 3 h, while use of pH 10 buffer led to 40 AP 24. Additional HPLC, HRMS and NMR studies supported that in addition to the 65% yield of 3, the end of reaction mixture also contained 12 AP (15% molar yield) of N,N dimer 23. After an aqueous Na₂S₂O₃ wash to quench the excess bleach, we subjected the resulting product-rich DCM layer to a variety of workup/isolation protocols to determine the fate of dimer 23. While direct addition of stoichiometric TfOH led to the rapid conversion of 23 to desmethyl pyrazole 14, the observation of ~10 LCAP dibromide 24 suggested that the strongly acidic conditions also led to the formation of an electrophilic bromide source, and the isolated 3•TfOH was only 55 LCAP (entry 2). In line with these results, while charging only 0.3 equiv HCl in IPA led to more controlled conversion of 23 to 14, ~4% over-bromination was still observed (entry 3).
Fortunately, the conversion of 23 to 14 also occurred upon addition of 0.5 equiv Et$_3$N, and under the basic conditions, no over-bromination was detected (entry 4). Based on our previous learnings from the Sandmeyer process that desmethyl 14 can selectively partition into aqueous HCl, we next performed 2 x 2 N HCl washes, followed by addition of TfOH and heptane as antisolvent to isolate 3•TfOH in 50% yield and 99.8 LCAP on 50 g scale. Utilizing this improved process, 182 kg 3•TfOH was prepared in 46-50% yield with excellent purity (99.8 LCAP).

Table 6. Investigating Oxidation Workup Protocol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Workup</th>
<th>Sample</th>
<th>3</th>
<th>23</th>
<th>24</th>
<th>14</th>
<th>25</th>
<th>Yield 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>end of reaction</td>
<td></td>
<td>85.1</td>
<td>12.1</td>
<td>0.29</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>65%*</td>
</tr>
<tr>
<td>2</td>
<td>TiOH addition to DCM layer</td>
<td>isolated 3•TfOH</td>
<td>55.2</td>
<td>&lt;0.05</td>
<td>10.3</td>
<td>22.6</td>
<td>0.72</td>
<td>ND*</td>
</tr>
<tr>
<td>3</td>
<td>0.3 equiv HCl to DCM layer</td>
<td>DCM layer</td>
<td>63.0</td>
<td>&lt;0.05</td>
<td>4.2</td>
<td>24.3</td>
<td>0.75</td>
<td>57%*</td>
</tr>
<tr>
<td>4</td>
<td>0.5 equiv Et$_3$N to DCM layer</td>
<td>DCM layer</td>
<td>68.1</td>
<td>&lt;0.05</td>
<td>0.30</td>
<td>30.2</td>
<td>&lt;0.05</td>
<td>65%*</td>
</tr>
<tr>
<td></td>
<td>after 2 x 2 N HCl washes</td>
<td>final DCM layer</td>
<td>90.4</td>
<td>&lt;0.05</td>
<td>0.43</td>
<td>6.6</td>
<td>0.72</td>
<td>61%*</td>
</tr>
<tr>
<td>4</td>
<td>TiOH addition then heptane</td>
<td>isolated 3•TfOH</td>
<td>99.8</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>0.16</td>
<td>&lt;0.05</td>
<td>50%*</td>
</tr>
</tbody>
</table>

*a In-process yield determined by HPLC.  b ND = not determined.  c Isolated yield.

Mechanistically, the formation of 14 is proposed to be due to competitive elimination pathways in N-halo intermediate 26, with desired Ha elimination leading to 3, and undesired Hb elimination affording iminium 28, which upon hydrolysis and oxidative dimerization generates 23 (Scheme 4a).
Et₃N during the workup then would lead to deprotonation/N-N bond cleavage to afford 1 equiv of both 14 and 28, the latter of which would undergo further oxidation to afford 2 equiv 14 per mole of 23. Deuterium labeling studies supported the proposed competitive deprotonations of Hₐ leading to 3 versus Hₐ leading to 14. As shown in Scheme 4B, by replacing the N-CH₃ group in 5 with N-CD₃ (29), which would have been expected to decrease the acidity of Hₐ versus Hₐ and favor the desired elimination pathway, the ratio of product:des-methyl impurity increased dramatically from 2.3:1 3:14 (starting from 5) to >20:1 30:14 (starting from 29), and 30 was isolated in 86% isolated yield.

Scheme 4. Proposed Oxidation Pathways

In conclusion, we have developed two scalable routes to N-methyl-3-bromo-5-methyl pyrazole (3). First, a Sandmeyer route involving a 3-step telescope from crotonitrile and methyl hydrazine, which proceeded through 3-amino pyrazole intermediate 2, led to 3•HCl with 99.9% HPLC purity in 19-28%
overall yield. Due to the genotoxic nature of 2, long-cycle time during the steam distillation of 3, low overall yield and sublimation challenges involving 3•HCl, we developed a second-generation route which leveraged a condensation, bromination, oxidation sequence starting from methyl crotonate and methyl hydrazine, as well as a crystallization protocol with triflic acid, to afford 3 as the higher melting 3•TfOH salt with 99.8% HPLC purity in an improved 38-42% overall yield.

Experimental section

General. The reactions were performed under a nitrogen atmosphere. All reagents were commercially available and used as received. GC or HPLC was used to monitor reaction progress. NMR analysis was performed on a Bruker DRX-400 or DRX-500 instrument.

Preparation of 18. To dichloromethane (1885 L, 13 L/kg) at ambient temperature was added bromine (346 kg, 2161 moles, 1.0 equiv). The resulting solution was then charged with HBr in acetic acid (33%, 26.1 L, 108 moles, 0.05 equiv) slowly over 2.5 h to maintain the internal temperature below 30 °C. A solution of crotonitrile (145 kg, 2161 moles, 1.0 equiv) in dichloromethane (290 L, 2 L/kg) was then added over 4-5 h maintaining the internal temperature between 30–35 °C. The reaction mixture was then aged for an additional 4-5 h before checking reaction conversion by HPLC (dilute 100 mg reaction mixture to 10 mL CH₃CN and analyze at 210 nm). Target conversion was <2.0% unreacted crotonitrile. Cooled reaction mixture to 25–30 °C and sequentially washed DCM layer with 10% aqueous sodium thiosulfate (580 L, 4 L/kg), 10% aqueous sodium bicarbonate (580 L, 4 L/kg) and water (870 L, 6 L/kg). The product-rich organic layer was then concentrated under vacuum at 40-45°C to dryness to afford 428 kg (91 wt%) of 18 as a crude clear yellow oil in 83 wt% corrected yield which was used without further purification.

Preparation of 2. Note: Nitrogen inertion should be utilized throughout all operations to prevent darkening of 2. However, darkening of 2 does not affect its’ downstream reactivity. To a 0 °C solution of
water (2.0 L, 4.16 L/kg) was sequentially charged 10 N NaOH (670 mL, 6.70 moles, 3.16 equiv) and methyl hydrazine (120 g, 2.61 moles, 1.23 equiv). Crude 18 (480.2 g, 2.12 moles, 1.0 equiv) was then added in portions over at least 2 h to maintain the internal temperature <10 °C. Checked pH after addition was complete. If pH was <12.5 charged additional 10 N NaOH. Checked reaction progress by HPLC after aging an additional 16 h at 0 °C. Target relative area percent was 18/2 < 2.0%. Charged toluene (500 mL, ~1 L/kg). Agitated for 15 min and then separated the phases. Extracted the product rich aqueous layer six times with DCM (6 x 750 mL, 6 x ~1.5 L/kg). Dried the combined product-rich DCM layers over Na2SO4, filtered and concentrated under vacuum to dryness to afford 196.4 g (97 LCAP, 98 wt%) of 2 as a yellow solid in 83% wt% corrected yield. The spectral data were consistent with previous reports.34

Preparation of 3•HCl. To a solution of water (609 L, 5 L/kg) and acetonitrile (1218 L, 10 L/kg) was charged copper(I) bromide (188.7 kg, 1315 moles, 1.2 equiv), followed by a solution of 2 (121.8 kg, 1096 moles, 1.0 equiv) in acetonitrile (609 L, 5 L/kg). The reaction mixture was cooled to 0-5 °C and charged with isoamyl nitrite (192.6 kg, 1644 moles, 1.5 equiv) over 8 h, keeping the internal temperature below 5 °C. Note: slow addition was required to minimize exotherm and allow venting of nitrogen gas. After an additional 30 min, reaction progress was checked by HPLC. Target relative area percent was 2/3 < 1.0%. The reaction mixture was then charged with water 1218 L (10 L/kg), agitated for at least 30 min at 20-25 °C, followed by celite (188.8 kg, 1.55 kg/kg). After agitating for 30 min, the layers were allowed to settle and the upper liquid layer was decanted into a new vessel. This washing/decanting of the celite residue was repeated two more times with 1:1 CH3CN:water (2 x 731 L, 2 x 6.0 L/kg). The celite mixture was then filtered and washed with water (243 L, 2.0 L/kg) and acetonitrile (122 L, 1.0 L/kg). Safety Note: testing showed that if the reaction slurry was concentrated without first adding water, a strong runaway exothermic event was possible. The combined CH3CN:water solutions were then subjected to constant-volume distillation, adding 5481 L (45 L/kg) water, under atmospheric pressure and collected product in aqueous distillate between 90-101 °C. Once distillation was complete, cooled to 20-25 °C and
washed combined aqueous distillates with MTBE (3 x 1219 L, 3 x 10 L/kg). Combined product-rich MTBE layers were then charged with Na₂SO₄, filtered, and washed with MTBE (50 L, 0.4 L/kg). The combined MTBE filtrates were then sequentially washed with 1 N aqueous HCl (600 L, ~5 L/kg), water (600 L, ~5 L/kg), concentrated to ~600 L (~5 L/kg) under atmospheric distillation conditions, and quantified to determine the in-process yield of 3 (31%). The final solution was then polish filtered and charged with 5 N HCl in IPA (136 L, 680 moles, 2.0 equiv with respect to in-process level of 3) over at least 1 h to maintain the internal temperature between 20-25 °C. After an additional 2-3 h, the resulting slurry was filtered, washed with MTBE (244 L, 2 L/kg) and dried under vacuum at 25-30 °C to afford 46.5 kg (99.9 LCAP, >99 wt%) of 3•HCl as a white solid in 27% yield; sublimes at 40 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 11.88 (s, 1 H), 6.07 (s, 1 H), 3.62 (s, 3 H), 2.16 (s, 3 H); ¹³C NMR (125 MHz, DMSO-d₆) δ 141.7, 123.0, 107.5, 36.5, 10.9; HRMS-ESI (m/z) calcd for C₅H₈N₂Br [M + H]⁺ 174.9864, found 174.9864.

**Preparation of 20•HBr.** To a mixture of isopropanol (46.5 L, 2.3 L/kg), and KOH (1.2 kg, 21.9 moles, 0.05 equiv) at 20-25 °C was charged methyl hydrazine (20.2 kg, 438 moles, 1.0 equiv). Reaction mass was then heated to 60-65 °C and visually checked to confirm all KOH had dissolved. Reaction mass was then cooled to 5-10 °C and slowly charged with *trans*-methyl crotonate (4, 46.1 kg, 460 moles, 1.05 equiv) over 2 h to maintain the internal temperature <25 °C. Note: strong exotherm observed. The reaction mixture was then agitated at 20-25 °C for 5 h before checking for reaction conversion by HPLC. Target relative area percent was 4/4+20+21 ≤ 11.0%. To a second reactor was charged isopropanol (188 L, 9.3 L/kg), cooled to 0-5°C and slowly charged acetyl bromide (59.3 kg, 482 moles, 1.1 equiv) over 2 h to maintain the internal temperature < 25 °C. Note: strong exotherm observed. After an additional 15 min, charged seeds of 20•HBr (808 g, 0.04 kg/kg) to 1st reactor and aged for 30 min. Charged HBr/IPA solution in 2nd reactor to 1st reactor over 2 h, maintaining the internal temperature in 1st reactor between 20-25 °C. Rinsed 2nd reactor with isopropanol (10 L, 0.5 L/kg) and transferred to 1st reactor. Aged resulting slurry
at 20-25 °C for 2 h and checked for desaturation. Target was <13 mg/mL or <1.5 wt% 20•HBr in mother liquor. Filtered slurry, sequentially washed cake with isopropanol (162 L, 8.0 L/kg) and MTBE (2 x 162 L, 2 x 8.0 L/kg) and dried under vacuum at 40 °C until LOD <1 wt% to afford 72.6 kg (99.9 LCAP, 99.8 wt%) of 20•HBr as a white solid in 85% yield; mp = 150-160°C; 1H NMR (400 MHz, D₂O) 4.15 (m, 1 H), 3.15 (s, 3 H), 3.06 (dd, J=8.0, 16.0 Hz, 1 H), 2.63 (dd, J= 8.0, 16.0 Hz, 1 H), 1.52 (d, J= 4.0 Hz, 3 H); 13C NMR (100 MHz, D₂O) δ 174.2, 65.9, 43.5, 36.0, 15.0; HRMS-ESI (m/z) calcd for C₅H₁₁ON₂ [M + H]+ 115.0866, found 115.0869.

**Preparation of 5.** To a mixture of 20•HBr (72.7 kg, 373 moles, 1.0 equiv) and tetraethylammonium bromide (23.3 kg, 111 moles, 0.3 equiv) in dichloromethane (218 L, 3.0 L/kg) at 20-25 °C was charged triethylamine (33.6 kg, 332 moles, 0.90 equiv) over 1 h maintaining the internal temperature <35 °C. The resulting reaction mixture was then cooled to 0-5 °C and charged with a solution of POBr₃ in dichloromethane [prepared with 137.8 kg (481 moles, 1.3 equiv) POBr₃ and 145 L (2.0 L/kg) dichloromethane] over 0.5 h, maintaining the internal temperature <15 °C. The reaction mixture was then warmed to 30 °C. The reaction mixture was then agitated at 30 °C for 6.5 h before checking for reaction conversion by HPLC. Note: HPLC analysis should utilize 0.10 M Me₄NOAc in MeOH as the sample prep diluent, as inconsistent results were observed using unbuffered CH₃CN or water. Target relative area percent was 20/20+5 ≤ 2.0%. To a separate reactor containing a 0-5 °C solution of water (1368 L, 19 L/kg) and NaOH (66.5 kg, 1663 moles, 4.5 equiv) was slowly charged the bulk reaction mixture, maintaining the internal temperature <20 °C, followed by a dichloromethane rinse (37 L, 0.5 L/kg). The resulting biphasic mixture was then warmed to 20-25 °C, agitated for 0.5 h, and the aqueous layer checked by pH. Target was 4 < pH < 5. If pH was <4, adjusted with 2 N aqueous NaOH; if pH was >5, adjusted with 2 N aqueous H₃PO₄. Split layers, and washed lower product-rich organic layer sequentially with 0.1 M NaH₂PO₄ (364 L, 5.0 L/kg) and water (364 L, 5.0 L/kg). Isolated 590 kg of final 5/DCM solution. Quantified wt% of DCM solution by 1H QNMR (d1 = 5 sec) using 1,2-dichloroethane as internal standard.
For 72.7 kg scale batch, final 5/DCM solution = 97.4 LCAP, 10.9 wt% and in-process yield = 97.6%.  

\(^1\)H NMR (500 MHz, CDCl\(_3\)) 3.16-3.07 (m, 1 H), 2.93 (dd, \(J = 9.4, 16.4\) Hz, 1 H), 2.3 (s, 3 H), 2.62 (dd, \(J = 13.9, 16.1\) Hz, 1 H), 1.27 (d, \(J = 6.3\) Hz, 3 H).

**Preparation of 3•TfOH.** To a 0-5 °C solution of potassium phosphate tribasic (265.7 kg, 1252 moles, 2.0 equiv), potassium bromide (37.3 kg, 313 moles, 0.5 equiv) and water (1253 L, 2.0 L/mole 5) was charged crude 5/DCM solution (1167 kg solution, 9.50 wt% 5 in DCM, 110.9 kg 5, 626 moles, 1.0 equiv). Aqueous bleach (770 kg, 10.6 wt% in water, 1096 moles, 1.75 equiv) was then added over 4-5 h, maintaining reaction mixture at 0-5 °C. The reaction mixture was then agitated at 0-5 °C for an additional 3 h before checking lower DCM layer for reaction conversion by HPLC. Target relative area percent was 5/3 ≤ 1.0%. The layers were split and the lower organic layer was then charged into a solution of sodium thiosulfate (198 kg, 1252 moles, 2.0 equiv) in purified water (1253 kg , 2.0 L/mole 5), maintaining the internal temperature between 0-5 °C. The layers were split, and the lower DCM layer was charged with triethylamine (31.7 kg, 313 moles, 0.5 equiv) over 0.5 h, warmed to 30-35 °C, and checked for reaction conversion by HPLC after 7 h. Target relative area percent was 23/23+3 ≤0.08. Note: relative response time (rrt) 23 = 1.50 with respect to 3. Cooled reaction mixture to 0-5 °C and charged 2 N HCl (438 L, 0.7 L/mole 5), maintaining the internal temperature between 0-10 °C. After agitating for 0.5 h, the layers were separated. The resulting product-rich lower organic layer was then washed with additional 2 x 2 N HCl (2 x 438 L, 2 x 0.7 L/mole 5), followed by water (438 L, 0.7 L/mole 5), all between 0-10 °C. Final DCM solution was then analyzed by HPLC to quantity in-process level of 3 to determine endpoint for concentration, and both TfOH and heptane charges. On 110.9 kg scale, total mass = 1017 kg; 91.31 LCAP; wt% = 5.74%; 58.4 kg 3; 334 moles; 53% in-process yield. Note: all remaining equivalents and volumes based on in-process level of 3. Concentrated DCM solution to ~290 L (5 L/kg) under atmospheric pressure. Charged dichloromethane (146 L, 2.5 L/kg) and concentrated under atmospheric pressure to ~290 L. After the concentration was complete, the reaction was sampled to ensure the water content (KF)
was <200 ppm. If KF > 200 ppm, charged additional dichloromethane and concentrated to ~290 L. Cooled solution to 20-25 °C and charged triflic acid (15.0 kg, 99.9 moles, 0.3 equiv), followed by 3•TfOH seeds (1.1 kg, 1.9 wt%). After aging for 0.5 h, the remaining triflic acid (35.0 kg, 233 moles, 0.7 equiv) was charged over 3-4 h. After an additional 0.5 h, heptane (99 L, 1.7 L/kg) was charged over 1-1.5 h, and after 2 h, the slurry was checked for desaturation. Target was <2.0 wt% 3•TfOH in mother liquor. If wt% was >2.0%, aged longer and resampled. Filtered slurry and washed reactor/cake with 30 volume % heptane in dichloromethane (117 L, 2 L/kg). Washed wet cake directly with 30 volume % heptane in dichloromethane (175 L, 3 L/kg) and then heptane (175 L, 3 L/kg), and dried under vacuum at 30 °C until loss-on-drying (LOD) <1 wt%. Isolated 93.2 kg (99.8 LCAP, 100 wt%, 46% yield) of 3•TfOH as an off-white solid; mp = 145°C; ¹H NMR (400 MHz, DMSO-d6) δ 11.73 (s, 1 H), 6.06 (s, 1 H), 3.62 (s, 3 H), 2.16 (s, 3 H); ¹³C NMR (100 MHz, DMSO-d6) δ 141.9, 123.2, 121.2 (q, J = 320 Hz), 107.6, 36.5, 10.9; HRMS-ESI (m/z) calcd for C₅H₈N₂Br [M + H]⁺ 174.9864, found 174.9865.

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We thank Dr. Antonio Ramirez for assistance with pKₐ modeling, Shella Tameze for conducting the Moisture Sorption Analysis, Dan Roberts for collecting pXRD data, Michael Peddicord and Jon Marshall for collecting high resolution mass spectra of all new compounds and NMR data for 22, Dr. Michael Schmidt for editorial comments, and the Chemical & Synthetic Development senior management for support during the preparation of the manuscript.

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Supporting Information Available

Further screening results for the bromination and oxidation sequence, characterization data for dimer 23, experimental details for the preparation of CD₃ derivative 30, and ¹H/¹³C NMR data for all compounds can be found in the Supporting Information. This information is available free of charge via the Internet at http://pubs.acs.org/.

References and Notes


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Complete removal of DCM was important as it can cause reaction stalling in the subsequent step. Isolated oil can also be dissolved in 1 L/kg toluene for use in subsequent cyclization.

As 2 was observed to slowly react with DCM, we also investigated extractions with CH$_3$CN. However, high salt loads were required to achieve phase splits, and only 40% of 2 was extracted.

While use of Cu(I)Br was critical, specific source of Cu(I)Br did not appear to impact reaction.

Without removing copper salts, concentrated reaction mass showed onset of major exotherm at 65-70 °C (ΔTad >300 °C) with an estimated ADT 24 and ADT 8 of 28 °C and 38 °C, respectively.

Scale-up attempts that excluded the celite filtration resulted in binding of the agitator and higher losses at the completion of the steam distillation.

Needed to run at atmospheric pressure. Much poorer recovery of 3 at lower pressures. While the acetonitrile/water distillation resulted in high concentrations of 3 in the distillate (on the order of 35 mg/mL), other solvent systems yielded similar outcomes. For example, both MTBE/water and a mesitylene system have been shown to distill the product.


pK$_a$ calculations were performed using a first-principles approach at the B3LYP/6-31G+(d) level of theory incorporating PCM corrections for water as the solvent. The pyrazoliyum-pyrazole acid-base pair was used as the experimental reference system. For leading references see: Ding, F.; Smith, J. M.; Wang, H. J. Org. Chem. 2009, 74, 2679.


The root cause for the increased regioselectivity using KOH

See Supporting Information for screening details.


In analogy to reactions with POCl₃, intermediates other than 22 may also be possible, see Arnott, E. A.; Chan, L. C.; Cox, B. G.; Meyrick, B.; Phillips, A. *J. Org. Chem.* **2011**, *76*, 1653.


Solubilities of NaH₂PO₄ and KH₂PO₄ in water = 86.9 g/100 mL and 22.6 g/100 mL, respectively. See [http://en.wikipedia.org/wiki/Solubility_table](http://en.wikipedia.org/wiki/Solubility_table)

Avoiding the use of VO(acac)₂ also prevented the need to control and quantitate vanadium levels, a Class 2A elemental metal.


See Supporting Information for complete analytical data.


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