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Strategy to Prepare 3-Bromo and 3-Chloropyrazoles

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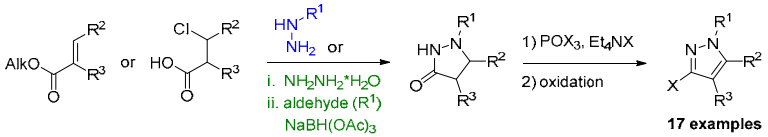


ABSTRACT

A general strategy to prepare substituted 3-bromo and 3-chloropyrazoles is described. The 3-step method involves condensation of crotonates or β-chloro carboxylic acids with hydrazines, followed by halogenation and oxidation. Several condensation and oxidation protocols were developed to enable preparation of a wide-variety of 3-halopyrazoles with good to excellent yields and regiocontrol.

INTRODUCTION

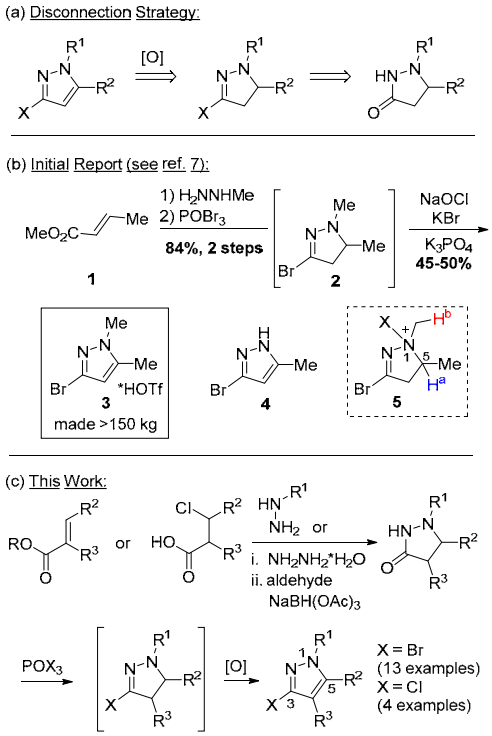
3-Bromo and 3-chloropyrazoles represent an important class of heterocyclic compounds due to their presence in a variety of biologically active compounds,[1] as well as their synthetic utility as starting materials for further functionalization.[2] Multiple methodologies have been reported to prepare 3-halopyrazoles, including: (1) electrophilic halogenation, (2) dehydroxyhalogenation, (3) Sandmeyer halogenodediazoniation, (4) cycloaddition, (5) N1 alkylation, and (5) palladium-catalyzed halogenation.[3] While successful in many cases, these methodologies often require harsh reaction conditions, leverage intermediates with genotoxicity concerns (e.g., use of aminopyrazole derivatives), or have limited substrate scope.

As part of a recent program that required kilogram quantities of a 3-bromopyrazole, we were attracted to an additional disconnection strategy involving sequential halogenation and oxidation of a starting pyrazolidin-3-one (Scheme 1a). While some examples of this strategy have been reported, the substrate scope was limited to aromatic side-chains.[4] In the few examples in which R^1 was alkyl, R^2 remained electron-withdrawing,[5] and when R^2 was not electron withdrawing, R^1 remained aromatic.[6] Our report describing the preparation of >150 kg **3** was the first example to sequentially halogenate/oxidize a pyrazolidin-3-one to prepare a 3-bromopyrazole with alkyl substitution at both R^1 and R^2 (Scheme 1b).[7,8] Interestingly, during our initial studies we observed competitive endo- versus exocyclic proton-elimination during oxidation (i.e., H^a versus H^b in **5**, Scheme 1), leading to **3** and des-methyl pyrazole **4**, respectively. This regioselectivity challenge supported why previous reports to prepare 3-halopyrazoles utilizing this methodology were focused on substrates that either lacked H^b protons (e.g., R^1 = aromatic), or contained electron-withdrawing groups at C(5) (e.g., R^2) to favor H^a elimination.

Herein, we report the first systematic study to examine the impact of substitution on the sequential condensation of crotonates or β–chloro carboxylic acids with hydrazines, followed by halogenation and oxidation of the resulting pyrazolidin-3-ones, to prepare 3-

halopyrazoles (Scheme 1c). We describe the utilization of both direct condensation and regioselective reductive amination conditions to prepare the requisite pyrazolidin-3-ones, along with multiple oxidation protocols to, for the first time, prepare a wide variety of 3-bromo- and 3-chloropyrazoles with good to excellent yields and excellent regiochemical control, utilizing a single synthetic strategy.

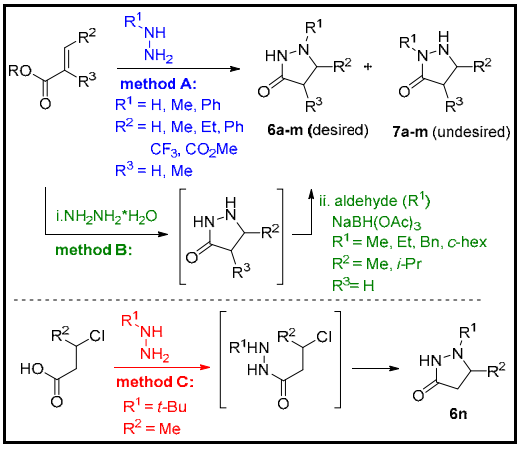
SCHEME 1

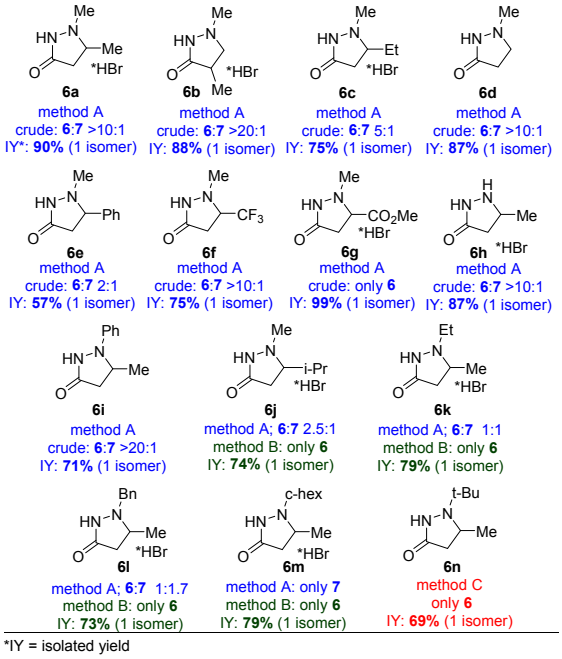


RESULTS AND DISCUSSION

Our efforts began by investigating the condensation of a variety of crotonates with various hydrazine derivatives. As shown in Scheme 2, using the conditions developed to prepare **3**, direct condensation (Method A) between methyl hydrazine (R^1 = Me), hydrazine monohydrate (R^1=H) or phenyl hydrazine (R^1=Ph), and either methyl crotonate (R=R^2=Me; R^3=H), methyl methacrylate (R=R^3=Me;R^2=H), or methyl acrylate (R=Me;R^2=R^3=H) proceeded with good (>10:1 crude) regioselectivity and high isolated yields (IY) as single regioisomers (**6a, 6b, 6d**, **6h, 6i**). Excellent regioselectivities were also observed with Method A using methylhydrazine to prepare the more electron–deficient crotonates **6f** (R^2=CF_3, R^3=H,) and **6g** (R^2=CO_2Me, R^3=H). However, the regioselectivity dropped upon increasing the steric bulk of the R^2 substituent. For example, when R^2= Et, R^3=H, the selectivity decreased to 5:1 (**6c**) and when R^2 = Ph, R^3 =H, the selectivity was only 2:1 (**6e**).[9] Despite the lower regioselectivities for these substrates, both **6c** and **6e** were isolated in good yields as single isomers after purification.

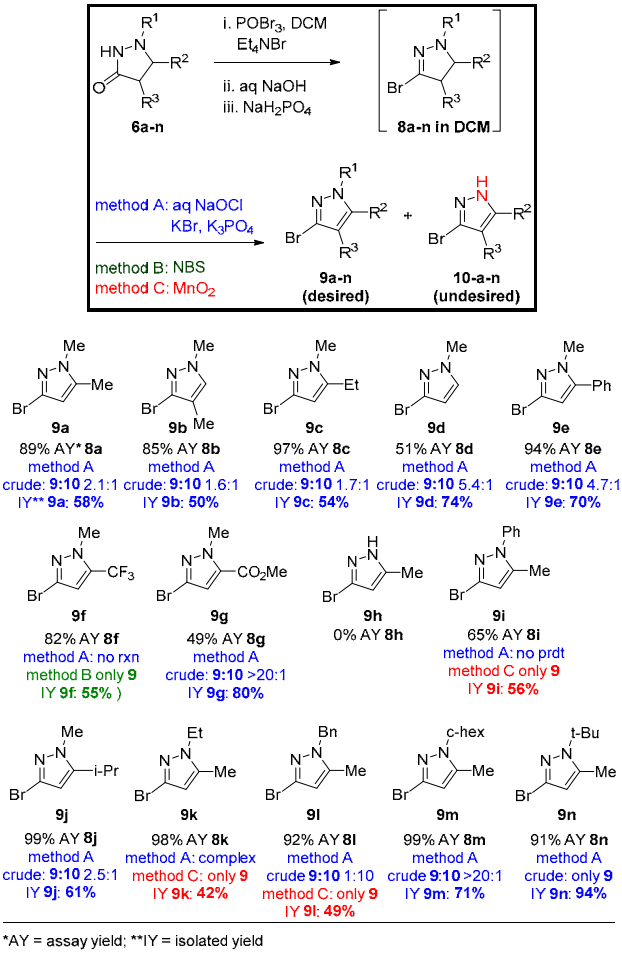
SCHEME 2. Condensation Approaches





As the size of either the *N*-R[1] or R[2] substituent increased further, the regioselectivities using Method A remained poor (**6j** and **6k**); and use of benzylhydrazine or cyclohexylhydrazine (**6l** and **6m**), favored the undesired regioisomer. Thus, to prepare substrates **6j-6m**, we developed a modified 2-step telescope (Method B) in which the crotonate esters were first condensed with hydrazine monohydrate, followed by regioselective reductive amination in the presence of $NaBH(OAc)_3$ and the requisite aldehydes.[10] Starting from isopropyl 4-methyl-2-pentenoate,[9] condensation with hydrazine monohydrate, followed by reductive amination with aqueous formaldehyde led to **6j** in 74% yield (2-steps) as a single regioisomer. Starting from hydrazine monohydrate and methyl crotonate, and using either acetaldehyde, benzaldehyde or cyclohexanone, led to **6k-6m**, respectively, in good yields as single regioisomers.[11] Lastly, to generate the *t*-butyl hydrazine derived substrate with the desired regioselectivity, we developed a third protocol (Method C) that involved initial amidation between *t*-butyl hydrazine and 3-chlorobutyric acid, followed by intramolecular chloride displacement to afford **6n** in 69% overall yield. While not shown in Scheme 1, methyl tiglate (i.e., R=R[2]=R[3]=Me) was unreactive with methyl hydrazine, and did not lead to significant product upon reaction with hydrazine hydrate.

SCHEME 3. Bromination and Oxidation Conditions



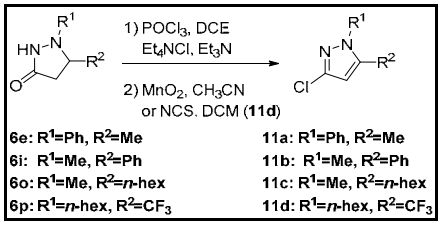
Continuing with the halogenation, with the exception of pyrazolidin-3-one **6h**[12] (R^1=R^3=H, R^2=Me), the bromination of substrates **6a-6n** with $POBr_3$ and Et_4NBr in DCM all proceeded in good to excellent yields (Scheme 3).[13] Following aqueous workup, the DCM solutions of 3-bromo dihydropyrazoles **8a-n** were quantified by ^{1}H NMR to obtain the reported in-process assay yields (AY).

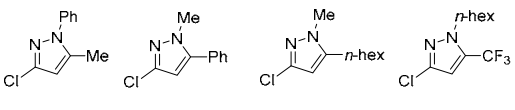
As previously disclosed (Scheme 1b),[7] the oxidation of **8a** using NaOCl/KBr[14] and K_3PO_4 under biphasic DCM/water conditions led to a 2.1:1 crude ratio of **9a**:**10a**. Following workup and purification, **9a** was isolated in 58% yield as a single compound. Comparable crude ratios of **9:10** (i.e., 1.6-2.5:1**)**, and isolated yields, were observed starting from **8b** (R^1=R^3=Me, R^2=H) and **8c** (R^1=Me, R^2=Et, R^3=H), as well as when the C(5) substituent was changed from methyl to *i*-Pr **(8j,** R^1=Me, R^2=*i*-Pr, R^3=H). On the other hand, when the C(5) methyl substituent was replaced with hydrogen (i.e., **8d**, R^1=Me, R^2=R^3=H) or phenyl (i.e., **8e**, R^1=Me, R^2=Ph, R^3=H), the crude ratio of **9d:10d** increased to approximately 5:1. Taken together, these results supported the hypothesis that increasing the accessibility and/or acidity of the C(5) proton favored the desired elimination of the activated *N*-halo intermediate (i.e., H_a vs H_b **5**, Scheme 1). This was further reinforced in the excellent selectivities observed using C(5) electron deficient compounds **8f** (R^1=Me, R^2=CF_3, R^3=H) and **8g (**R^1=Me, R^2=CO_2Me, R^3=H**)**. With **8g**, the crude ratio of **9g**:**10g** was >20:1, and **9g** was isolated in 80% yield. Substrate **8f** proved too electron deficient to react with NaOCl, but oxidation with NBS afforded **9f** in 55% yield, and **10b** was not detected.[15] As expected, increasing the steric bulk of the *N*-substituent from *N*-methyl to *N*-cyclohexyl also led to a significantly improved crude ratio of **9m:10m**

(>20:1), and **9m (**R^1= *c*-hex, R^2=Me, R^3=H) was isolated in 71% yield. For *N*-t-Bu substrate **8n**, which lacked competing protons for elimination, **9n (**R^1=*t*-Bu, R^2=Me, R^3=H) was isolated in 94% yield. On the contrary, *N*-benzyl substrate **8l (**R^1=Bn, R^2=Me, R^3=H) led to a crude 1:10 ratio of **9l:10l**, presumably due to the phenyl ring increasing the acidity of the exocyclic benzylic protons and favoring debenzylation. For **8l**, alternative MnO_2 oxidation conditions were utilized to isolate **9l** in 49% yield. Interestingly, under the MnO_2 conditions, des-benzyl impurity **10l** was not observed. The MnO_2 oxidation conditions were also utilized for substrates **8i** and **8k**, possessing either an *N*-phenyl or *N*-ethyl substituent, as the corresponding oxidations with NaOCl failed to yield the desired product (**9i,** R^1=Ph, R^2=Me, R^3=H), or produced a complex reaction mixture (**9k,** R^1=Et, R^2=Me, R^3=H). With MnO_2, **9i** and **9k** were isolated in 56% and 42% yield, respectively.

In addition to 3-bromopyrazoles, we also investigated application of this methodology to the preparation of 3-chloro derivatives, (Scheme 4) and while successful, we observed some important differences. The chlorinations of pyrazolidin-3-ones **6e,i,o,p** with $POCl_3$ were far slower than the corresponding brominations, necessitating a change of solvent to 1,2-dichloroethane (DCE) and a temperature increase to 60 °C (vs 30 °C). The subsequent oxidations to the pyrazoles were also ineffective (no reaction) under the NaOCl conditions, while utilization of potassium persulfate led to decomposition, DBU/NCS to no reaction, and DDQ to slow and complex reaction mixtures. The optimal oxidation reagents were found to be excess MnO_2, and in the case of highly electron-deficient substrate **6p**, NCS. Finally, the product 3-chloropyrazoles were inherently more volatile than the bromopyrazoles. For example, while the analogous C3-chloropyrazole of **9a** (R^1=R^2=Me, R^3=-H) was effectively prepared by the conditions in Scheme 4, it was isolated in only 20% yield due to losses during concentration. Based on this observation, we opted to prepare the higher molecular weight analogues **11c** and **11d** bearing an *n*-hexyl (vs Me) substituent. Despite these differences, in analogy to the 3-bromo series, 3-chloropyrazoles containing both alkyl and phenyl substituents at both N(1) and C(5) were prepared in moderate to good yields (**11a-c**), as well as a C(5) $–CF_3$ group (**11d**).

SCHEME 4. Application to 3-Chloropyrazoles





CONCLUSION

In summary, we have disclosed a systematic study of the impact of substitution on a general 3-step approach to prepare substituted 3-bromo- or 3-chloropyrazoles based on the condensation of either crotonate esters or β-chloro carboxylic acids with substituted hydrazines, followed by sequential halogenation and oxidation. Most importantly, we identified multiple condensation and oxidation protocols to enable the preparation of a wide-variety of substituted products utilizing a single synthetic strategy, which would have been difficult to achieve with previously published methodologies.

EXPERIMENTAL SECTION

General. The reactions were performed under a nitrogen atmosphere. All reagents were commercially available and used as received. MnO_2 (activated, ~85%, <5 μm) was purchased from Sigma-Aldrich and used without further activation. Commercial tetraethylammonium chloride was dried in a 110 °C oven for 24 h, cooled to room temperature and ground to a fine powder before use. TLC or HPLC was used to monitor reaction progress. SiO_2 purification was performed using either traditional columns (100-200 mesh) or a Teledyne ISCO purification system. NMR analysis was performed on a Bruker DRX-400 or DRX-500 instrument, and all ^{13}C spectra were proton-decoupled L/kg refer to liters of solvent charged per kg of the limiting reagent in each experiment.

General Condensation Procedure to Prepare Pyrazolidin-3-one HBr Salts. *1,5-Dimethylpyrazolidin-3-one hydrobromide (6a).* To a mixture of isopropanol (4.7 mL, 2.3 L/kg), and KOH (0.12 g, 2.14 mmoles, 0.05 equiv) at 20-25 °C was charged methyl hydrazine (2.02 g, 43.8 mmoles, 1.0 equiv). The reaction mass was then heated to 60-65 °C and visually checked to confirm all KOH had dissolved. The reaction mass was then cooled to 5-10 °C and slowly charged with *trans*-methyl crotonate (4.83 g, 48.2 mmoles, 1.10 equiv), maintaining the internal temperature <25 °C. Note: strong exotherm observed. The reaction mixture was then agitated at 20-25 °C for 5 h. To a second RBF containing isopropanol (18.8 mL, 9.3 L/kg) at 0-5°C was **s**lowly charged acetyl bromide (5.93 g, 48.2 mmoles, 1.1 equiv) over ~30 min., maintaining the internal temperature < 25 °C. Note: strong exotherm observed. The HBr/IPA solution was then charged to reaction mixture over ~2 h, maintaining the internal temperature between 20-25 °C. The RBF containing the HBr/IPA solution was then rinsed with isopropanol (1.0 mL, 0.5 L/kg) and transferred to reaction mixture. The resulting slurry was then aged at 20-25 °C for 2 h. The slurry was then filtered, sequentially washed cake with isopropanol (16.2 mL, 8.0 L/kg) and MTBE (2 x 16.2 mL, 2 x 8.0 L/kg), and dried under vacuum at 40 °C to afford 7.69 g (99.9 LCAP, 99.8 wt%) of **6a** as a white solid in 90% yield; mp = 150-160ºC; ^1H NMR (400 MHz, D_2O) δ 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); ^{13}C NMR (100 MHz, D_2O) δ 174.2, 65.9, 43.5, 36.0, 15.0; HRMS-ESI (*m/z*) calcd for $C_5H_{11}ON_2$ $[M + H]^+$ 115.0866, found 115.0869.

1,4-Dimethylpyrazolidin-3-one hydrobromide (6b). Starting from methyl hydrazine (4.00 g, 85.1 mmoles, 1.0 equiv) and methyl methacrylate (9.46 g, 93.5 mmoles, 1.10 equiv), with 20 h reaction time, isolated 14.7 g of **6b** as a white solid in 88% yield; mp = 185-188ºC; ^1H NMR (500 MHz, D_2O, 1:1 mixture of rotamers) δ 4.42 (app t, *J* = 10 Hz, 1 H), 3.96-3.90 (m, 1 H), 3.89-3.82 (m, 1 H), 3.39 (app t, *J*= 10 Hz, 1 H), 3.27-3.17 (m , 1 H), 3.19 (d, *J*= 10 Hz, 3 H), 3.13-3.07 (m, 1 H), 1.24 (d, *J*= 4.0 Hz, 3 H); ^{13}C NMR (125 MHz,

D_2O, 1:1 mixture of rotamers) δ 177.3, 60.9, 60.4, 45.7, 45.2, 35.8, 34.0, 12.9, 12.3; HRMS-ESI (*m/z*) calcd for $C_5H_{11}N_2O$ $[M + H]^+$ 115.0866, found 115.0867.

5-Ethyl-1-methylpyrazolidin-3-one hydrobromide (6c). Starting from methyl hydrazine (4.00 g, 85.1 mmoles, 1.0 equiv) and methyl 2-pentenoate (10.9 g, 93.5 mmoles, 1.10 equiv), with 23 h reaction time, isolated 13.3 g of **6c** as a white solid in 75% yield; mp = 155-157°C; ^{1}H NMR (500 MHz, D_2O) δ 4.10–4.00 (m, 1 H), 3.18 (s, 3 H), 3.09 (dd, *J*= 5.0, 15 Hz, 1 H), 2.69 (dd, *J* = 5.0, 15 Hz, 1 H), 2.09-1.97 (m, 1 H), 1.83-1.77 (m, 1 H), 0.97 (t, *J*= 10 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 174.2, 70.8, 44.5, 34.1, 23.4, 9.2; HRMS-ESI (*m/z*) calcd for $C_6H_{13}N_2O$ $[M + H]^+$ 129.1022, found 129.1022.

Methyl 2-methyl-5-oxopyrazolidine-3-carboxylate hydrobromide (6g). Starting from methyl hydrazine (4.00 g, 85.1 mmoles, 1.0 equiv) and dimethyl maleate (13.6 g, 93.5 mmoles, 1.10 equiv), with 16 h reaction time, isolated 20.2 g of **6g** as a white solid in 99% yield; mp = 193-195°C; ^{1}H NMR (500 MHz, D_2O) δ 4.51 (dd, *J*= 5.0, 10.0 Hz, 1 H), 3.76 (s, 3 H), 3.21 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.94 (s, 3 H), 2.88 (dd, *J*= 5.0, 15.0 Hz, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 172.5, 168.1, 66.6, 54.2, 46.2, 32.1; HRMS-ESI (*m/z*) calcd for $C_6H_{11}N_2O_3$ $[M + H]^+$ 159.0764, found 159.0763.

5-Methylpyrazolidin-3-one hydrobromide (6h). To a solution of methanol (100 mL, 2.3 L/kg), and hydrazine hydrate (5.26 g, 64 wt%, 105 mmoles, 1.0 equiv) at 20-25 °C was charged *trans*-methyl crotonate (11.3 g, 110 mmoles, 1.05 equiv). The reaction mixture was then heated to reflux, and after 5 h, concentrated to dryness, followed by charging with isopropanol (13 mL, 2.5 L/kg). Analogous isolation as **6a** afforded 16.5 g of **6h** as a white solid in 87% yield; mp = 195-198°C; ^{1}H NMR (500 MHz, D_2O) δ 4.43-4.35 (m, 1 H), 2.96 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.56 (dd, *J*= 5.0, 15.0 Hz, 1 H), 1.50 (d, *J*= 10.0 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 175.7, 55.5, 35.6, 16.2; HRMS-ESI (*m/z*) calcd for $C_4H_9N_2O$ $[M + H]^+$ 101.0709, found 101.0713.

General Condensation Procedure to Prepare Pyrazolidin-3-one Freebase. *1-Methylpyrazolidin-3-one (6d).* To a mixture of isopropanol (85 mL, 3.8 L/kg), and KOH (0.84 g, 13.0 mmoles, 0.05 equiv) at 20-25 °C was charged methyl hydrazine (15.58 g, 331.4 mmoles, 1.3 equiv). The reaction mass was then heated to 60-65 °C and visually checked to confirm all KOH had dissolved. The reaction mass was then cooled to 5-10 °C and slowly charged methyl acrylate (22.2 g, 255 mmoles, 1.0 equiv), maintaining the internal temperature <25 °C. Note: strong exotherm observed. The reaction mixture was then agitated at 20-25 °C for 16 h. The reaction mixture was then concentrated to dryness, charged with toluene (2 x 50 mL, 2 x 2.3 L/kg), concentrating after each charge. Purification by ISCO chromatography (330 g column, flow rate 200 mL/min, gradient 0% MeOH in EtOAc for 1 CV, then to 25% MeOH over 1 CV and 25% till end, collected 25 mL fractions) afforded 22.3 g of **6d** as a pale yellow oil in 87% yield . R_f = 0.20 (20% MeOH in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (br s, 1 H), 3.50-3.00 (m, 2 H), 2.61 (s, 3 H), 2.62-2.50 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 53.7, 46.5, 30.2; HRMS-ESI (*m/z*) calcd for $C_4H_9N_2O$ $[M + H]^+$ 101.0709, found 101.0712.

1-Methyl-5-phenylpyrazolidin-3-one (6e). Starting from isopropanol (30 mL, 1.2 L/kg), KOH (0.365 g, 6.44 mmoles, 0.05 equiv), methyl hydrazine (9.08 g, 193 mmoles, 1.5 equiv) and isopropyl cinnamate (25.0 g, 129 mmoles, 1.0 equiv), with 3.5 day reaction time at 65 °C, isolated 12.9 g of **6e** as a white solid in 57% yield after ISCO purification (330 g column, flow rate 200 mL/min, gradient 100% EtOAc for 5 CV, then to 10% MeOH in EtOAc over 2 CV, collected 25 mL fractions). R_f = 0.30 (100% EtOAc); mp = 118-120°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5 H), 3.96 (m, 1 H), 2.96 (dd, *J*= 7.5, 15.0 Hz, 1 H), 2.65 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.56 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 138.7, 128.7, 128.2, 127.3, 70.0, 44.7, 40.1; HRMS-ESI (*m/z*) calcd for $C_{10}H_{13}N_2O$ $[M + H]^+$ 177.1022, found 177.1022.

1-Methyl-5-(trifluoromethyl)pyrazolidin-3-one (6f). Starting with isopropanol (11.5 mL, 2.3 L/kg), KOH (0.301 g, 5.31 mmoles, 0.05 equiv), methyl hydrazine (5.00 g, 106 mmoles, 1.0 equiv) and 4,4,4-trifluorocrotonate (18.1 g, 112 mmoles, 1.05 equiv), with 0.5 h reaction time at 20-25 °C, isolated 14.1 g of **6f** as a white solid in 75% yield after ISCO purification (330 g column, flow rate 200 mL/min, gradient 100% hexanes for 1 CV, then to 100% EtOAc over 1 CV, collected 25 mL fractions). R_f = 0.25 (6:1 EtOAc:hexanes); mp = 95-97°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65-3.45 (m, 1 H), 3.07 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.74 (s, 3 H), 2.56 (dd, *J*= 5.0, 15.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 124.2 (q, *J*= 278 Hz), 64.4 (q, *J*= 31 Hz), 48.3, 29.5; HRMS-ESI (*m/z*) calcd for $C_5H_8F_3N_2O$ $[M + H]^+$ 169.0583, found 169.0582.

5-Hexyl-1-methylpyrazolidin-3-one (6o). Starting with methanol (4.6 mL, 2.3 L/kg), KOH (32 mg, 0.58 mmoles, 0.05 equiv), methyl hydrazine (671 uL, 12.7 mmoles, 1.10 equiv) and methyl 2-nonenoate (2.00 g, 11.50 mmoles, 1.00 equiv.), with 24 h reaction time at 50 °C, isolated 974 mg of **6o** as a light yellow oil in 46% yield after flash column chromatography over basic alumina (0 to 7.5% isopropanol in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 2.90 (quintet, *J* = 6.9 Hz, 1 H), 2.74 (dd, *J* = 8.1, 16.4 Hz, 1 H), 2.53 (s, 3 H), 2.07 (dd, *J* = 3.8, 16.7 Hz, 1 H), 1.53-1.69 (m, 9 H), 0.83 (app t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7; 65.5, 45.9, 35.7, 33.7, 31.6, 29.0, 25.9, 22.4, 13.9; HRMS-ESI (*m/z*) calcd for $C_{10}H_{21}N_2O$ $[M + H]^+$ 185.1648, found 185.1647.

5-Methyl-1-phenylpyrazolidin-3-one (6i). To a 0-5 °C solution of toluene (202 mL, 13.5 L/kg), phenylhydrazine (15.0 g, 135 mmoles, 1.0 equiv) and methyl crotonate (17.9 g, 175 mmoles, 1.3 equiv) was charged potassium *t*-butoxide (20 wt% in THF, 75.5 g, 135 mmoles, 1.0 equiv) over ~1 h. After 7.5 h, added kicker charge of potassium *t*-butoxide (20 wt% in THF, 7.55 g, 135 mmoles, 0.1 equiv). The reaction mixture was then warmed to 20-25 °C, and after 14 h, charged with acetic acid (~7 mL) until apparent pH = 7. Water (100 mL, 6.7 L/kg) was then added, followed by an additional ~3 mL AcOH to adjust pH to 7. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to afford 24 g of a crude solid. The solids were then charged with MTBE (25 mL), agitated for 2.5 h and filtered. The solids were then washed with MTBE (2 x 25 mL), and dried in vacuum oven at 45 °C to afford 16.8 g of **6i** as a pale yellow solid in 71% yield; mp = 123-125°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (br s, 1 H), 7.33-7.27 (m, 2 H), 7.08-7.03 (m, 3 H), 4.02-3.96 (m, 1 H), 2.91 (dd, *J*= 5.0, 15.0 Hz, 1 H), 2.03 (app d, *J*= 15.0 Hz, 1 H), 1.46 (d, *J*= 5.0 Hz, 3 H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 151.0, 129.1, 123.0, 116.7, 63.5, 36.3, 21.4; HRMS-ESI (*m/z*) calcd for $C_{10}H_{13}N_2O$ $[M + H]^+$ 177.1022, found 177.1020.

General 2-Step Condensation/Reductive Amination Procedure. *5-Isopropyl-1-methylpyrazolidin-3-one hydrobromide (6j).* To a 20-25 °C solution of isopropanol (76 mL, 15.8 L/kg) and hydrazine hydrate (4.80 g, 50.5 wt%, 75.6 mmoles, 1.0 equiv) was charged isopropyl 4-methyl-2-pentenoate (13.0 g, 83.2 mmoles, 1.10 equiv). The reaction mixture was then heated to 80 °C, and after 40 h, concentrated to dryness, followed by charging 1,2-dichloroethane (~40 mL) and reconcentrating to dryness to remove residual IPA. Residue was then charged with 1,2-dichloroethane (151 mL, 31.5 L/kg) and formaldehyde (37 wt% in water, 6.80 g, 83.8 mmoles, 1.10 equiv). Reaction mixture was then placed in a cold water bath and charged sodium triacetoxyborohydride (67.5 g, 303 mmoles, 4.0 equiv) to control exotherm to <35 °C. Gas evolution also observed. The thick reaction mixture was then warmed to 20-25 °C, and after 1 h 45 min, charged with DCM (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). Gas evolution observed. Charged 5 N NaOH (~50 mL) to adjust pH to 8-9. Split layers and washed aqueous layer with DCM (3 x 50 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated to dryness, and charged isopropanol (10 mL, 2.1 L/kg). To a second RBF containing isopropanol (34 mL, 7.1 L/kg), at 0-5°C was **s**lowly charged acetyl bromide (10.3 g, 82.9 mmoles, 1.1 equiv) over ~10 min., maintaining the internal temperature <25 °C. Note: strong exotherm observed. The HBr/IPA solution was then charged to reaction solution over ~1 h, maintaining the internal temperature between 20-25 °C. The RBF containing the HBr/IPA solution was then rinsed with isopropanol (4.0 mL, 0.8 L/kg) and transferred to reaction mixture. The resulting slurry was then aged at 20-25 °C for 1.5 h, filtered, sequentially washed with isopropanol (18 mL, 3.8 L/kg) and MTBE (2 x 18 mL, 2 x 3.8 L/kg) and dried under vacuum at 50 °C to afford 12.4 g of **6j** as a white solid in 74% yield (2-steps); mp =159-161°C; ^{1}H NMR (500 MHz, D_2O) δ 4.12-4.07 (m, 1 H), 3.22 (s, 3 H), 3.15-3.05 (m, 1 H), 2.83-2.73 (m, 1 H), 2.85-2.70 (m, 1 H), 1.02 (d, *J*= 5.0 Hz, 3 H), 0.97 (d, *J*= 5.0 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 174.2, 74.6, 46.4, 31.2, 29.3, 18.2, 16.3; HRMS-ESI (*m/z*) calcd for $C_7H_{15}N_2O$ $[M + H]^+$ 143.1179, found 143.1179.

1-Ethyl-5-methylpyrazolidin-3-one hydrobromide (6k). Starting with methanol (72 mL, 2.3 L/kg), hydrazine hydrate (3.79 g, 64 wt%, 75.8 mmoles, 1.0 equiv) and *trans*-methyl crotonate (8.52 g, 83.4 mmoles, 1.10 equiv), with 5 h reaction time at reflux, followed by 1,2-dichloroethane (152 mL, 40.1 L/kg), acetaldehyde (8.15 g, 182 mmoles, 2.4 equiv) and sodium triacetoxyborohydride (25.4 g, 114 mmoles, 1.5 equiv), with 3 h reaction time at 20-25 °C and then additional acetaldehyde (2.8 g, 63 mmoles, 0.8 equiv). and 1 h reaction time, along with 15 x 75 mL DCM washed during workup to fully back extract product, isolated 12.5 g of **6k** as a white solid in 79% yield (2-steps) after HBr salt formation; mp = 158-160°C; ^{1}H NMR (500 MHz, D_2O) δ 4.34-4.27 (m, 1 H), 3.63-3.56 (m, 1 H), 3.45-3.38 (m, 1 H), 3.11 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.59 (dd, *J* = 5.0, 15.0 Hz, 1 H), 1.52 (d, *J*= 5.0 Hz, 3 H), 1.30 (t, *J* = 5.0 Hz, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 174.6, 63.4, 53.5, 35.7, 16.3, 8.5; HRMS-ESI (*m/z*) calcd for $C_6H_{13}N_2O$ $[M + H]^+$ 129.1022, found 129.1023.

1-Benzyl-5-methylpyrazolidin-3-one hydrobromide (6l). Started with methanol (95 mL, 2.3 L/kg), hydrazine hydrate (5.00 g, 64 wt%, 99.9 mmoles, 1.0 equiv) and *trans*-methyl crotonate (11.2 g, 110 mmoles, 1.10 equiv), with 5 h reaction time at reflux, followed by 1,2-

dichloroethane (200 mL, 40 L/kg), benzaldehyde [11.7 g, 110 mmoles, 1.1 equiv, age 8 h before adding $NaBH(OAc)_3$] and sodium triacetoxyborohydride (33.4 g, 150 mmoles, 1.5 equiv), with 17 h reaction time at 20-25 ºC. Benzaldehyde [21.07 g, 10.0 mmoles, 0.10 equiv, age 8 h before $NaBH(OAc)_3$ kicker] and sodium triacetoxyborohydride (33.4 g, 150 mmoles, 1.5 equiv) kickers were then added, and after an additional 17 h, charged additional benzaldehyde (21.07 g, 10.0 mmoles, 0.10 equiv), aged 2 h, and sodium triacetoxyborohydride (33.4 g, 150 mmoles, 1.5 equiv). After 20 h, added additional sodium triacetoxyborohydride (4.46 g, 20 mmoles, 0.2 equiv). After an additional 21 h, completed workup to afford 19.8 g of **6l** as a white solid in 73% yield (2-steps) after HBr salt formation; mp = 184-186ºC; ^{1}H NMR (500 MHz, D_2O) δ 7.5-7.25 (m, 5 H), 4.68-4.50 (m, 1 H), 4.50-4.40 (m, 1 H), 4.40-4.25 (m, 1 H), 2.80-2.70 (m, 1 H), 2.45-2.35 (m, 1 H), 1.45-1.30 (m, 3 H); ^{13}C NMR (125 MHz, D_2O) δ 174.5, 131.6, 130.0, 129.5, 127.3, 62.9, 61.5, 35.6, 16.6; HRMS-ESI (*m/z*) calcd for $C_{11}H_{15}N_2O$ $[M + H]^+$ 191.1179, found 191.1177.

1-Cyclohexyl-5-methylpyrazolidin-3-one hydrobromide (6m). Starting with methanol (72 mL, 2.3 L/kg), hydrazine hydrate (3.79 g, 64 wt%, 75.8 mmoles, 1.0 equiv) and *trans*-methyl crotonate (8.52 g, 83.4 mmoles, 1.10 equiv), with 5 h reaction time at reflux, followed by 1,2-dichloroethane (152 mL, 40.1 L/kg), cyclohexanone (8.36 g, 83.5 mmoles, 1.1 equiv) and sodium triacetoxyborohydride (25.4 g, 114 mmoles, 1.5 equiv), with 6.5 h reaction time at 20-25 ºC, isolated 15.7 g of **6m** as a white solid in 79% yield (2-steps) after HBr salt formation; mp = 189-191ºC; ^{1}H NMR (500 MHz, D_2O) δ 4.56-4.49 (m, 1 H), 3.57-3.28 (m, 1 H), 3.12 (dd, *J*= 10.0, 15.0 Hz, 1 H), 2.53 (dd, *J*= 5.0, 20.0 Hz, 1 H), 2.06-2.00 (m, 2 H), 1.87-1.84 (m, 2 H), 1.64-1.61 (m, 1 H),1.52 (d, *J*= 5.0 Hz, 3 H), 1.45-1.25 (m, 4 H), 1.15-1.07 (m, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 174.5, 67.7, 60.6, 36.7, 26.9, 25.7, 24.3, 24.1, 23.9, 17.8; HRMS-ESI (*m/z*) calcd for $C_{10}H_{19}N_2O$ $[M + H]^+$ 183.1492, found 183.1491.

1-Hexyl-5-(trifluoromethyl)pyrazolidin-3-one (6p). Starting with methanol (20 mL), hydrazine monohydrate (658 µL, 13.60 mmoles, 1.10 equiv) and methyl 4,4,4-trifluorocrotonate (1.62 mL, 12.30 mmoles, 1.00 equiv), with 0.5 h reaction time at 20-25ºC, followed by 1,2-dichloroethane (20 mL), hexanal [2.25 mL, 18.50 mmoles, 1.50 equiv, aged 2.5 h before adding $NaBH(OAc)_3$] and sodium triacetoxyborohydride (4.71 g, 21.60 mmoles, 1.75 equiv), with 15 h reaction time at 20-25 ºC, isolated 2.68 g of **6p** as a thick oil that slowly crystallized to a waxy solid in 91% yield (2-steps) after ISCO chromatography (0 to 50% ethyl acetate in hexanes gradient; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1 H), 3.64 (dqd, *J* = 2.9, 7.4, 10.2 Hz, 1 H), 3.04 (dd, *J* = 9.9, 17.7 Hz, 1 H), 2.83 (t, *J* = 7.6 Hz, 2 H), 2.50 (dd, *J* = 2.9, 17.8 Hz, 1 H), 1.46-1.59 (m, 2 H), 1.26-1.42 (m, 6 H), 0.90 (app t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 124.6 (q, *J* = 279.6 Hz), 62.5 (q, *J* = 31.0 Hz), 61.1, 31.4, 29.2, 26.8, 26.3, 22.5, 13.9; HRMS-ESI (*m/z*) calcd for $C_{10}H_{18}F_3N_2O$ $[M + H]^+$ 239.1366, found 239.1364.

Method for 2-Step Amidation/Cyclization Route. *1-tert-Butyl-5-methylpyrazolidin-3-one (6n).* To a solution of DCM (41 mL, 8.2 L/kg) and 3-chlorobutyricacid (5.00 g, 40.8 mmoles, 1.0 equiv) was charged 1 drop of DMF. Cooled solution to 0-5 ºC and charged oxalyl chloride (4.3 mL, 50 mmoles, 1.2 equiv) over 1 min. Allowed reaction mixture to warm to 20-25 ºC during which time slow gas evolution was observed. After 8 h, concentrated to dryness, followed by charging and reconcentrating with DCM (2 x 40 mL). Charged

residue with DCM (41 mL, 8.2 L/kg) and quantified by ^{1}H NMR using 1,2-dichloroethane as internal standard to verify in-process DCM solution contained 7.88 wt% acid chloride intermediate**.** Based on solution mass = 59.61 g, solution yield = 82%. ^{1}H NMR of acid chloride (400 MHz, $CDCl_3$) δ 4.46-4.37 (m, 1 H), 3.30 (app dddd, *J*= 7.8, 17.2, 17.2, 17.2 Hz, 2 H), 1.58 (d, *J*= 6.6 Hz, 3 H); To *t*-butylhydrazine hydrochloride (5.29 g, 42.5 mmoles, 2.0 equiv) and sodium bicarbonate (3.57 g, 42.5 mmoles, 2.0 equiv) was charged DCM (38 mL, 1 L/kg) and water (38 mL, 1 L/kg). After aging at 20-25 °C for 5 min, during which time minor gas evolution was slowly observed, cooled to 0-5 °C and began charging acid chloride/DCM solution (38.0 g, 7.88 wt%, 21.2 mmoles, 1.0 equiv) via syringe pump over 3.5 h. After an additional 15 min., warmed reaction mixture to 40 °C, and after an additional 24 h, cooled to 20-25 °C. Split layers (pH aq layer = 2; saved product rich aqueous layer) and washed DCM layer with 0.5 M aqueous H_3PO_4 (2 x 15 mL). To the combined aqueous layers, charged DCM (20 mL), followed by the slow addition of 45 wt% aqueous KOH (9.5 mL), keeping internal temperature <28 °C, to increase pH to 12. Split layers, and washed aqueous layer with DCM (4 x 20 mL). Dried combined product-rich DCM layers over $MgSO_4$, filtered, concentrated to dryness and purified by ISCO chromatography (80 g column, flow rate 60 mL/min, gradient 100% DCM for 1 CV, then to 10% MeOH over 6 CV) to afford 2.80 g of **6n** as a white solid in 84% yield; R_f = 0.44 (10% MeOH in DCM); mp = 84-86°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (br s, 1 H), 3.55-3.47 (m, 1 H), 2.81 (dd, *J*= 9.1, 17.0 Hz, 1 H), 1.86 (dd, *J*= 1.8, 17.0 Hz, 1 H), 1.17 (d, *J*= 6.6 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 58.7, 51.3, 37.9, 25.3, 23.6; HRMS-ESI (*m/z*) calcd for $C_8H_{17}N_2O$ $[M + H]^+$ 157.1335, found 157.1335.

General Method for Halogenation. *3-Bromo-1,5-dimethyl-4,5-dihydro-1H-pyrazole (8a).* To a mixture of **6a** (10.00 g, 50.73 mmoles, 1.0 equiv) and tetraethylammonium bromide (3.20 g, 15.2 mmoles, 0.3 equiv) in dichloromethane (30 mL, 3.0 L/kg) at 20-25 °C was charged triethylamine (4.62 g, 45.7 mmoles, 0.90 equiv) over 2-3 minutes, maintaining the internal temperature <35 °C. The resulting reaction mixture was then cooled to 0-5 °C and charged with a solution of $POBr_3$ in dichloromethane [prepared with 18.9 g (65.9 mmoles, 1.3 equiv) $POBr_3$ and 20 mL (2.0 L/kg) dichloromethane] over 5-10 minutes, maintaining the internal temperature <20 °C. The reaction mixture was then warmed to 30 °C and agitated for 5 h. In a separate reactor containing a 0-5 °C solution of water (190 mL, 3.7 L/mole) and NaOH (9.14 g, 228 mmoles, 4.5 equiv) was slowly charged the bulk reaction mixture, maintaining the internal temperature <20 °C, followed by a dichloromethane rinse (5 mL, 0.1 L/mole). The resulting biphasic mixture was then warmed to 20-25 °C, agitated for 0.5 h, and the aqueous layer checked by pH. Target: 4 < pH < 5. If pH <4, adjusted with 2 N aqueous NaOH; if pH >5, adjusted with 2 N aqueous H_3PO_4. Split layers, and washed lower product-rich organic layer sequentially with 0.1 M NaH_2PO_4 (50 mL, 0.975 L/mole) and water (50 mL, 0.975 L/mole). Isolated 91.36 g of final **8a**/DCM solution. Quantified wt% by ^{1}H QNMR (d1 = 5 sec) using 1,2-dichloroethane as internal standard. For 10 g scale batch, final **8a**/DCM solution = 8.78 wt% and in-process yield = 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16-3.07 (m, 1 H), 2.93 (dd, *J*= 9.4, 16.4 Hz, 1 H), 2.30 (s, 3 H), 2.62 (dd, *J*= 13.9, 16.1 Hz, 1 H), 1.27 (d, *J*= 6.3 Hz, 3 H).

3-Bromo-1,4-dimethyl-4,5-dihydro-1H-pyrazole (8b). Starting from **6b** (10.00 g, 51.27 mmoles, 1.0 equiv), tetraethylammonium bromide (3.23 g, 15.4 mmoles, 0.3 equiv), triethylamine (4.67 g, 46.2 mmoles, 0.90 equiv), DCM (30 mL, 3 L/kg), and $POBr_3$ (19.11 g, 66.66 mmoles, 1.3 equiv) in DCM (20 mL, 2 L/kg), with a DCM (10 mL, 1 L/kg) rinse, 7 h reaction time, and aqueous workup, isolated 95.25 g of final **8b**/DCM solution. Final **8b**/DCM solution = 8.06 wt% and in-process yield = 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (dd, *J*= 10.0, 10.0 Hz, 1 H), 3.16-3.08 (m, 1 H), 2.75 (s, 3 H), 2.61 (dd, *J*= 10.0, 10.0 Hz, 1 H), 1.16 (d, *J* = 5.0 Hz, 3 H).

3-Bromo-5-ethyl-1-methyl-4,5-dihydro-1H-pyrazole (8c). Starting from **6c** (10.72 g, 51.27 mmoles, 1.0 equiv), tetraethylammonium bromide (3.23 g, 15.4 mmoles, 0.3 equiv), triethylamine (4.67 g, 46.2 mmoles, 0.90 equiv), DCM (30 mL, 2.8 L/kg), and $POBr_3$ (19.11 g, 66.66 mmoles, 1.3 equiv) in DCM (20 mL, 1.9 L/kg), with a DCM (10 mL, 0.93 L/kg) rinse, 4 h reaction time, and aqueous workup, isolated 100.58 g of final **8c**/DCM solution. Final **8c**/DCM solution = 9.45 wt% and in-process yield = 97%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01-2.90 (m, 2 H), 2.73 (s, 3 H), 2.65 (dd, *J*= 15.0, 15.0 Hz, 1 H), 1.80-1.73 (m, 1 H), 1.56-1.47 (m, 1 H), 0.89 (t, *J*= 10.0 Hz, 3 H).

3-Bromo-5-isopropyl-1-methyl-4,5-dihydro-1H-pyrazole (8j). Starting from **6j** (10.04 g, 45.00 mmoles, 1.0 equiv), tetraethylammonium bromide (2.84 g, 13.5 mmoles, 0.3 equiv), triethylamine (4.09 g, 40.04 mmoles, 0.90 equiv), DCM (27 mL, 2.7 L/kg), and $POBr_3$ (16.78 g, 58.53 mmoles, 1.3 equiv) in DCM (18 mL, 1.8 L/kg), with a DCM (9 mL, 0.89 L/kg) rinse, 3.5 h reaction time, and aqueous workup, isolated 92.85 g of final **8j**/DCM solution. Final **8j**/DCM solution = 9.88 wt% and in-process yield = 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02-2.97 (m, 1 H), 2.82-2.70 (m, 2 H), 2.74 (s, 3 H), 1.97-1.91 (m, 1 H), 0.91 (d, *J*= 6.9 Hz, 3 H), 0.87 (d, *J*= 6.7 Hz, 3 H).

3-Bromo-1-ethyl-5-methyl-4,5-dihydro-1H-pyrazole (8k). Starting from **6k** (10.72 g, 51.27 mmoles, 1.0 equiv), tetraethylammonium bromide (3.23 g, 15.4 mmoles, 0.3 equiv), triethylamine (4.67 g, 46.2 mmoles, 0.90 equiv), DCM (30 mL, 2.8 L/kg), and $POBr_3$ (19.11 g, 66.66 mmoles, 1.3 equiv) in DCM (20 mL, 1.9 L/kg), with a DCM (10 mL, 0.93 L/kg) rinse, 3 h reaction time, and aqueous workup, isolated 110.07 g of final **8k**/DCM solution. Final **8k**/DCM solution = 8.72 wt% and in-process yield = 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35-3.22 (m, 1 H), 3.05-2.92 (m, 2 H), 2.76-2.70 (m, 1 H), 2.61 (dd, *J*= 10.0, 15.0 Hz, 1 H), 1.26 (d, *J*= 5.0 Hz, 3 H), 1.21 (t, *J*= 10.0 Hz, 3 H).

1-Benzyl-3-bromo-5-methyl-4,5-dihydro-1H-pyrazole (8l). Starting from **6l** (10.00 g, 36.88 mmoles, 1.0 equiv), tetraethylammonium bromide (2.33 g, 11.1 mmoles, 0.3 equiv), triethylamine (3.36 g, 33.2 mmoles, 0.90 equiv), DCM (22 mL, 2.2 L/kg), and $POBr_3$ (13.75 g, 47.96 mmoles, 1.3 equiv) in DCM (14.4 mL, 1.4 L/kg), with a DCM (8 mL, 0.8 L/kg) rinse, 3 h reaction time, and aqueous workup, isolated 79.67 g of final **8l**/DCM solution. Final **8l**/DCM solution = 10.77 wt% and in-process yield = 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.20 (m, 5 H), 3.58 (AB_q, 2 H, $\Delta\delta_{AB}$ = 67.5, J_{AB} = 12.5 Hz), 3.31-3.23 (m, 1 H), 2.88 (dd, *J*= 10.0, 15.09 Hz, 1 H), 2.58 (dd, *J*= 15.0, 16.0 Hz, 1 H), 1.16 (d, *J*= 5.0 Hz, 3 H).

3-Bromo-1-cyclohexyl-5-methyl-4,5-dihydro-1H-pyrazole (8m). Starting from **6m** (10.00 g, 38.00 mmoles, 1.0 equiv), tetraethylammonium bromide (2.40 g, 11.4 mmoles, 0.3 equiv), triethylamine (3.46 g, 34.2 mmoles, 0.90 equiv), DCM (22 mL, 2.2 L/kg), and $POBr_3$ (14.20 g, 49.53 mmoles, 1.3 equiv) in DCM (15 mL, 1.5 L/kg), with a DCM (8 mL, 0.8 L/kg) rinse, 3 h reaction time, and aqueous workup, isolated 74.11 g of final **8m**/DCM solution. Final **8m**/DCM solution = 12.54 wt% and in-process yield = 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64-3.56 (m, 1 H), 2.96 (dd, *J*= 10.0, 20.0 Hz, 1 H), 2.72-2.65 (m, 1 H), 2.57 (dd, *J*= 12.5, 17.5 Hz, 1 H), 1.87-1.77 (m, 4 H), 1.66-1.58 (m, 2 H), 1.31-1.20 (m, 1 H), 1.24 (d, *J*= 5.0 Hz, 3 H), 1.20-1.09 (m, 3 H).

Methyl 3-bromo-1-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (8g). Starting from **6g** (10.00 g, 92 wt%, 38.48 mmoles, 1.0 equiv), tetraethylammonium bromide (2.43 g, 11.6 mmoles, 0.3 equiv), triethylamine (8.96 g, 88.5 mmoles, 2.3 equiv), DCM (22.5 mL, 2.25 L/kg), and $POBr_3$ (14.34 g, 50.02 mmoles, 1.3 equiv) in DCM (15 mL, 1.5 L/kg), with a DCM (8 mL, 0.8 L/kg) rinse, 3 h reaction time, and aqueous workup, isolated 82.12 g of final **8g**/DCM solution. Final **8g**/DCM solution = 5.08 wt% and in-process yield = 49%. ~10% oxidized product **9g** was also observed by HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.69-3.66 (m, 1 H), 3.27 (dd, *J*= 12.6, 16.9 Hz, 1 H), 3.13 (dd, *J*= 11.1, 16.9 Hz, 1 H), 2.85 (s, 3 H).

3-Bromo-1-methyl-4,5-dihydro-1H-pyrazole (8d). Starting from **6d** (7.91 g, 79.0 mmoles, 1.0 equiv), tetraethylammonium bromide (4.98 g, 23.7 mmoles, 0.3 equiv), DCM (57 mL, 7.2 L/kg), and $POBr_3$ (29.4 g, 103 mmoles, 1.3 equiv) in DCM (29 mL, 3.7 L/kg), 19 h reaction time, and analogous aqueous workup as **8a** but using water (273 mL, 34.5 L/kg) and 85% KOH (23.5 g, 356 mmoles, 4.5 equiv), keeping pH >10 to prevent product decomposition, isolated 147.87 g of final **8d**/DCM solution. Final **8d**/DCM solution = 4.42 wt% and in-process yield = 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34-3.16 (m, 2 H), 3.06-2.95 (m, 2 H), 2.87 (br s, 3 H).

3-Bromo-1-methyl-5-phenyl-4,5-dihydro-1H-pyrazole (8e). Starting from **6e** (5.02 g, 28.5 mmoles, 1.0 equiv), tetraethylammonium bromide (1.80 g, 8.56 mmoles, 0.3 equiv), DCM (17 mL, 3.4 L/kg), and $POBr_3$ (10.60 g, 36.97 mmoles, 1.3 equiv) in DCM (11 mL, 2.2 L/kg), 2 h reaction time, and analogous aqueous workup as **8a**, but using water (106 mL, 21.1 L/kg) and NaOH (6.27 g, 157 mmoles, 5.5 equiv) isolated 58.78 g of final **8e**/DCM solution. Final **8e**/DCM solution = 10.9 wt% and in-process yield = 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5 H), 4.05 (dd, *J*= 10.0, 15.0 Hz, 1 H), 3.21 (dd, *J*= 10.0, 15.0 Hz, 1 H), 3.00 (dd, *J*= 15.0, 15.0 Hz, 1 H), 2.70 (s, 3 H).

3-Bromo-1-methyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole (8f). Starting from **6f** (5.00 g, 29.7 mmoles, 1.0 equiv), tetraethylammonium bromide (1.90 g, 9.04 mmoles, 0.3 equiv), DCM (30 mL, 6 L/kg), and $POBr_3$ (11.10 g, 38.72 mmoles, 1.3 equiv) in DCM (15 mL, 3 L/kg), 9 h reaction time, and analogous aqueous workup as **8a**, but using water (95 mL, 19 L/kg), NaOH (4.16 g, 104 mmoles, 3.5 equiv) and adding aqueous NaOH to reaction mixture, isolated 103.38 g of final **8f**/DCM solution. Final **8f**/DCM solution = 5.45 wt% and in-process yield = 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69-3.62 (m, 1 H), 3.25 (dd, *J* = 11.4, 17.5, Hz, 1 H), 3.15 (dd, *J*= 11.7, 17.5 Hz, 1 H), 2.92 (br s, 3 H).

3-Bromo-5-methyl-1-phenyl-4,5-dihydro-1H-pyrazole (8i). Starting from **6i** (10.00 g, 56.75 mmoles, 1.0 equiv), tetraethylammonium bromide (3.20 g, 15.2 mmoles, 0.3 equiv), DCM (57 mL, 5.7 L/kg), triethylamine (5.22 g, 51.1 mmoles, 0.9 equiv) and $POBr_3$ (21.2 g, 73.9 mmoles, 1.3 equiv) in DCM (29 mL, 2.9 L/kg), 8 h reaction time at 0-5 °C, and aqueous workup, isolated 493.40 g of final **8i**/DCM solution, containing some other minor byproducts. Final **8i**/DCM solution = 1.80 wt% and in-process yield = 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (app br s, 2 H), 7.04 (app br s, 2 H), 6.88 (app br s, 1 H), 4.38 (app br s, 1 H), 3.42 (app br s, 1 H), 2.82 (app br s, 1 H), 1.32 (app br s, 3 H).

3-Bromo-1-tert-butyl-5-methyl-4,5-dihydro-1H-pyrazole (8n). Starting from **6n** (2.40 g, 15.4 mmoles, 1.0 equiv), tetraethylammonium bromide (0.97 g, 4.6 mmoles, 0.3 equiv), DCM (16 mL, 6.7 L/kg), and $POBr_3$ (5.75 g, 20.1 mmoles, 1.3 equiv) in DCM (8 mL, 3.3 L/kg), 4.5 h reaction time, and analogous aqueous workup as **8a**, but using water (48 mL, 20 L/kg) and NaOH (2.15 g, 53.7 mmoles, 3.5 equiv), isolated 41.36 g of final **8n**/DCM solution. Final **8n**/DCM solution = 7.37 wt% and in-process yield = 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69-3.61 (m, 1 H), 3.18 (dd, *J*= 11.4, 17.3 Hz, 1 H), 2.59 (dd, *J*= 9.6, 17.3 Hz, 1 H), 1.30 (d, *J*= 6.0 Hz, 3 H), 1.16 (s, 9 H).

General Method for Oxidation using NaOCl/KBr. *3-Bromo-1,5-dimethyl-1H-pyrazole (9a).* To a 0-5 °C solution of potassium phosphate tribasic (9.52 g, 44.8 mmoles, 2.0 equiv**),** potassium bromide (1.33 g, 11.2 mmoles, 0.5 equiv**)** and water (45 mL, 2.0 L/mole **8a**) was charged crude **8a**/DCM solution (44.20 g solution, 8.78 wt% **8a** in DCM, 21.9 mmoles, 1.0 equiv). Aqueous bleach (27.2 g, 10.5 wt% in water, 38.4 mmoles, 1.75 equiv) was then added via syringe pump subsurface using a Teflon tube as the needle over 2.5-3 h, maintaining reaction mixture at 0-5 °C. The reaction mixture was then agitated at 0-5 °C for an additional 2.5 h before charging water (8 mL, 0.36 L/mole **8a**) to fully dissolve solids. Split layers, and the lower organic phase was charged into a 0-5 °C solution of 0.1 M aqueous sodium thiosulfate (45 mL, 2.0 L/mole **8a**), maintaining the internal temperature between 0-5 °C. Split layers, and the lower DCM phase was charged with triethylamine (1.12 g, 11.0 mmoles, 0.5 equiv), warmed to 30-35 °C, and after 15.5 h, cooled to 20-25 °C, dried over $MgSO_4$, filtered and concentrated to dryness. Purified residue (2.1 : 1 **9a:10a**) by SiO_2 (5 cm diameter column, 6 in SiO_2, flow rate = 1 in/min, gradient = 8:1 hex:EtOAc for 1 CV then 4:1 for 4 CV) to afford 2.22 g of **9a** as a colorless oil in 58% yield which solidified upon standing; R_f **9a** = 0.15 (10% EtOAc in hexanes); mp = 35-38°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1 H), 3.74 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ140.7, 124.0, 107.6, 36.2, 10.9; HRMS-ESI (*m/z*) calcd for $C_5H_8BrN_2$ $[M + H]^+$ 174.9865, found 174.9864.

3-Bromo-1,4-dimethyl-1H-pyrazole (9b). Starting from potassium phosphate tribasic (9.08 g, 42.8 mmoles, 2.0 equiv**),** potassium bromide (1.27 g, 10.7 mmoles, 0.5 equiv**),** water (43 mL, 2.0 L/mole **8b**), **8b**/DCM solution (47.00 g solution, 8.06 wt% **8b** in DCM, 21.4 mmoles, 1.0 equiv), aqueous bleach (26.5 g, 10.5 wt% in water, 37.4 mmoles, 1.75 equiv added over 3 h, then after an additional 2 h, 1.53 g, 2.16 mmoles, 0.10 equiv kicker added over 12 min and 1 h further reaction time), and triethylamine (1.08 g, 10.6 mmoles, 0.5 equiv with 14 h @ 30-35 °C), isolated 1.86 g of **9b** as a colorless oil in 50% yield after SiO_2 purification (5 cm diameter column, 9

in SiO_2, flow rate = 1 in/min, gradient = 8:1 hex:EtOAc for 1 CV, 4:1 for 4 CV, 1:1 till end); R_f **9b** = 0.18 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 3.82 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.0, 126.9, 116.4, 39.2, 8.9; HRMS-ESI (*m/z*) calcd for $C_5H_8BrN_2$ $[M + H]^+$ 174.9865, found 174.9865.

3-Bromo-5-ethyl-1-methyl-1H-pyrazole (9c). Starting from potassium phosphate tribasic (9.09 g, 42.8 mmoles, 2.0 equiv**),** potassium bromide (1.27 g, 10.7 mmoles, 0.5 equiv**),** water (43 mL, 2.0 L/mole **8c**), **8c**/DCM solution (43.30 g solution, 9.45 wt% **8c** in DCM, 21.4 mmoles, 1.0 equiv), aqueous bleach (25.0 g, 10.5 wt% in water, 35.3 mmoles, 1.65 equiv added over 3 h, then after an additional 2 h, 1.53 g, 2.16 mmoles, 0.10 equiv kicker added over 5 min and 1 h further reaction time), and triethylamine (1.09 g, 10.7 mmoles, 0.5 equiv with 30 h @ 30-35 °C), isolated 2.20 g of **9c** as a colorless oil in 54% yield after SiO_2 purification (6.5 cm diameter column, 9 in SiO_2, flow rate = 1 in/min, gradient = 8:1 hex:EtOAc for 1 CV, 4:1 for 3.5 CV, 1:1 till end); R_f **9c** = 0.21 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1 H), 3.70 (s, 3 H), 2.55 (q, *J*= 7.5 Hz, 2 H), 1.21 (t, *J*= 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 124.0, 105.9, 36.1, 18.7, 12.3; HRMS-ESI (*m/z*) calcd for $C_6H_{10}BrN_2$ $[M + H]^+$ 189.0022, found 189.0021.

3-Bromo-1-methyl-1H-pyrazole (9d). Starting from potassium phosphate tribasic (4.90 g, 23.1 mmoles, 2.0 equiv**)**, potassium bromide (0.69 g, 5.8 mmoles, 0.5 equiv**),** water (23 mL, 2.0 L/mole **8d**), **8d**/DCM solution (90.00 g solution, 2.09 wt% **8d** in DCM, 11.5 mmoles, 1.0 equiv), aqueous bleach (11.1 g, 10.8 wt% in water, 16.1 mmoles, 1.4 equiv added over 3 h, then after an additional 1.5 h, 1.6 g, 2.3 mmoles, 0.20 equiv kicker added over 25 min, then after an additional 0.5 h, 2.0 g, 2.9 mmoles, 0.25 equiv kicker added over 20 min, then after an additional 1 h, 1.6 g, 2.3 mmoles, 0.20 equiv kicker added over 1 min, then after an additional 1 h, 1.6 g, 2.3 mmoles, 0.20 equiv kicker added in one portion and 30 min further reaction time), and triethylamine (0.590 g, 5.77 mmoles, 0.5 equiv with 14 h @ 30-35 °C), isolated 1.38 g of **9d** as a pale orange oil in 74% yield after ISCO purification (120 g column, flow rate 85 mL/min, gradient 100% hexanes for 1 CV, then to 10% EtOAc over 1 CV, 10% EtOAc for 1 CV then to 20% EtOAc over 1 CV, 20% EtOAc for 4 CV, then to 35% EtOAc over 1 CV, 35% EtOAc for 4 CV then to 65% EtOAc over 1 CV); R_f **9d** = 0.15 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*= 5.0 Hz, 1 H), 6.21 (d, *J*= 5.09 Hz, 1 H), 3.85 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.0, 124.9, 108.4, 39.3; HRMS-ESI (*m/z*) calcd for $C_4H_6BrN_2$ $[M + H]^+$ 160.9709, found 160.9708.

*3-Bromo-1-methyl-5-phenyl-1H-pyrazole (9e)***.** Starting from potassium phosphate tribasic (9.09 g, 42.8 mmoles, 2.0 equiv), potassium bromide (1.27 g, 10.7 mmoles, 0.5 equiv), water (43 mL, 2.0 L/mole **8e**), **8e**/DCM solution (48.9 g solution, 10.46 wt% **8e** in DCM, 21.4 mmoles, 1.0 equiv), aqueous bleach (22.8 g, 10.5 wt% in water, 32.2 mmoles, 1.5 equiv added over 3 h, then after an additional 2.5 h, 3.79 g, 5.35 mmoles, 0.25 equiv kicker added over 15-20 min, and 30 min further reaction time), and triethylamine (1.09 g, 10.7 mmoles, 0.5 equiv with 16 h @ 30-35 °C), isolated 3.54 g of **9e** as a pale yellow oil in 70% yield after ISCO purification (220 g column, flow rate 150 mL/min, gradient 100% hexanes for 1 CV, then to 10% EtOAc over 1 CV, 10% EtOAc for 3.5 CV then to 100% EtOAc over 15 CV); R_f **9e** = 0.30 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.38 (m, 5 H), 6.32 (s, 1 H), 3.86 (s, 3 H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 145.8, 129.3, 129.0, 128.8, 128.7, 124.8, 108.3, 37.6; HRMS-ESI (*m/z*) calcd for $C_{10}H_{10}BrN_2$ $[M + H]^+$ 237.0022, found 237.0020.

Methyl 3-bromo-1-methyl-1H-pyrazole-5-carboxylate (9g). Starting from potassium phosphate tribasic (6.34 g, 29.9 mmoles, 2.0 equiv**),** potassium bromide (0.89 g, 7.5 mmoles, 0.5 equiv), water (30 mL, 2.0 L/mole **8g**), **8g**/DCM solution (65.0 g solution, 5.08 wt% **8g** in DCM, 14.9 mmoles, 1.0 equiv), aqueous bleach (12.4 g, 10.8 wt% in water, 18.0 mmoles, 1.2 equiv added over 3 h, with no additional age time required), and triethylamine (0.76 g, 7.5 mmoles, 0.5 equiv with 17 h @ 30-35 °C), isolated 2.63 g of **9g** as a colorless oil in 80% yield after ISCO purification (120 g column, flow rate 85 mL/min, gradient 100% hexanes for 1 CV, then to 50% DCM over 1 CV, 50% DCM for 4 CV then to 65% DCM over 1 CV); R_f **9g** = 0.26 (50% DCM in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1 H), 4.14 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 134.0, 124.1, 113.3, 52.2, 39.8; HRMS-ESI (*m/z*) calcd for $C_6H_8BrN_2O_2$ $[M + H]^+$ 218.9764, found 218.9760.

3-Bromo-5-isopropyl-1-methyl-1H-pyrazole (9j). Starting from potassium phosphate tribasic (9.09 g, 42.8 mmoles, 2.0 equiv**),** potassium bromide (1.27 g, 10.7 mmoles, 0.5 equiv), water (43 mL, 2.0 L/mole **8j**), **8j**/DCM solution (44.4 g solution, 9.88 wt% **8j** in DCM, 21.4 mmoles, 1.0 equiv), aqueous bleach (26.6 g, 10.5 wt% in water, 37.5 mmoles, 1.75 equiv added over 3 h, with 1 h additional age time), and triethylamine (1.09 g, 10.7 mmoles, 0.5 equiv with 7 days @ 35-40 °C), isolated 2.64 g of **9j** as an orange oil in 61% yield after ISCO purification (220 g column, flow rate 150 mL/min, gradient 100% hexanes for 1 CV, then to 10% EtOAc over 1.5 CV, 10% EtOAc for 3 CV then to 100% EtOAc over 10 CV); R_f **9j** = 0.31 (4:1 hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1 H), 3.73 (s, 3 H), 2.88 (sept, *J*= 10.0 Hz, 1 H), 1.20 (d, *J*= 10.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 124.1, 104.4, 36.2, 25.3, 21.9; HRMS-ESI (*m/z*) calcd for $C_7H_{12}BrN_2$ $[M + H]^+$ 203.0178, found 203.0177.

3-Bromo-1-cyclohexyl-5-methyl-1H-pyrazole (9m). Starting from potassium phosphate tribasic (5.43 g, 25.6 mmoles, 2.0 equiv**)**, potassium bromide (0.76 g, 6.39 mmoles, 0.5 equiv), water (26 mL, 2.0 L/mole **8m**), **8m**/DCM solution (25.00 g solution, 12.54 wt% **8m** in DCM, 12.79 mmoles, 1.0 equiv), and aqueous bleach (13.6 g, 10.5 wt% in water, 19.2 mmoles, 1.5 equiv added over 3 h, with no additional age time), isolated 2.20 g of **9m** as a colorless oil in 71% yield after ISCO purification (120 g column, flow rate 85 mL/min, gradient 100% hexanes for 2 CV, then to 10% EtOAc over 3 CV, 10% EtOAc for 4 CV then to 20% EtOAc over 3 CV). Note: triethylamine treatment was not performed with this substrate; R_f **9m** = 0.39 (10:1 hex:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1 H), 3.93-3.85 (m, 1 H), 2.24 (s, 3 H), 1.98-1.84 (m, 6 H), 1.70-1.68 (m, 1 H), 1.41-1.22 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 124.1, 107.2, 57.9, 32.6, 25.6, 25.0, 10.9; HRMS-ESI (*m/z*) calcd for $C_{10}H_{16}BrN_2$ $[M + H]^+$ 243.0491, found 243.0488.

3-Bromo-1-tert-butyl-5-methyl-1H-pyrazole (9n). Starting from potassium phosphate tribasic (5.00 g, 23.6 mmoles, 2.0 equiv), potassium bromide (0.700 g, 5.88 mmoles, 0.5 equiv), water (23.5 mL, 2.0 L/mole **8n**), **8n**/DCM solution (35.0 g solution, 7.37 wt% **8n** in DCM, 11.8 mmoles, 1.0 equiv), and aqueous bleach (10.7 g, 9.80 wt% in water, 14.1 mmoles, 1.2 equiv added over 3 h, with 2 h

additional age time), and triethylamine (0.60 g, 5.9 mmoles, 0.5 equiv with 15 h @ 30-35 °C), isolated 2.40 g of **9n** as a pale yellow oil in 94% yield after ISCO purification (80 g column, flow rate 50 mL/min, gradient 100% hexanes for 1 CV, then to 5% MeOH over 4 CV, 5% MeOH for 4 CV then to 20% MeOH); R_f **9n** = 0.58 (5% MeOH in hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1 H), 2.41 (s, 3 H), 1.61 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ140.2, 122.5, 110.3, 60.7, 30.0, 14.5; HRMS-ESI (*m/z*) calcd for $C_8H_{14}BrN_2$ $[M + H]^+$ 217.0335, found 217.0334.

Oxidation using NBS. *3-Bromo-1-methyl-5-(trifluoromethyl)-1H-pyrazole (9f).* To a 0-5 °C solution of crude **8f**/DCM solution (41.2 g solution, 7.11 wt% **8f** in DCM, 12.7 mmoles, 1.0 equiv) was charged *N*-bromosuccinimide (1.48 g, 8.26 mmoles, 0.65 equiv). After 30 min, charged additional *N*-bromosuccinimide (1.48 g, 8.26 mmoles, 0.65 equiv). After 4 h, charged additional *N*-bromosuccinimide (0.46 g, 2.6 mmoles, 0.20 equiv). After 17 h, charged 0.1 M aqueous $Na_2S_2O_3$ (30 mL, 2.4 L/mole **8f**) in 5 mL aliquots, maintaining internal temperature <10 °C, followed by additional solid $Na_2S_2O_3$ (2 g in 2 x 1 g portions). Charged 5 N NaOH (3 mL) to adjust pH to 10, followed by water (30 mL, 2.4 L/mole **8f**). Split layers, washed lower DCM layer with saturated aqueous $NaHCO_3$ (20 mL, 1.6 L/mole **8f**), dried over $MgSO_4$, filtered, concentrated and purified by ISCO chromatography (80 g column, flow rate 60 mL/min, gradient 100% hexanes for 2 CV, then to 10% EtOAc over 4 CV, 10% EtOAc till end) to afford 1.59 g of **9f** as a colorless oil in 55% yield; R_f = 0.30 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1 H), 3.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8 (q, *J*= 40 Hz), 124.5, 119.0 (q, *J*= 268 Hz), 110.0, 38.4; HRMS-ESI (*m/z*) calcd for $C_5H_5BrF_3N_2$ $[M + H]^+$ 228.9583, found 228.9582.

General Method for Oxidation using MnO_2. *3-Bromo-5-methyl-1-phenyl-1H-pyrazole (9i).* The crude **8i**/DCM solution (250 g solution, 1.80 wt% **8i** in DCM, 18.8 mmoles, 1.0 equiv) was concentrated to dryness, charged toluene (65 mL, 3.5 L/mole **8i**) and manganese dioxide (16.4 g, 189 mmoles, 10.0 equiv), and warmed to 100-105 °C. After 5 days, cooled to 20-25 °C filtered reaction mixture through a pad of celite (16 g, 0.85 g/mole **8i**) wetted with 1:1 DCM:2-propanol and washed with 1:1 DCM:2-propanol (3 x 50 mL portions). Combined filtrate was then further polish filtered, rinsing with 1:1 DCM:2-propanol (50 mL), and concentrated to dryness. Purification by ISCO chromatography (220 g column, flow rate 150 mL/min, gradient 100% hexanes for 1 CV, then to 20% EtOAc over 4 CV, 20% EtOAc for 4 CV then to 35% EtOAc over 2 CV) led to 2.51 g of **9i** as an orange oil in 56% yield; R_f = 0.42 (5:1 hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.35 (m, 5 H), 6.22 (s, 1 H), 2.31 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 138.9, 129.0, 128.0, 126.9, 124.8, 109.4, 12.2; HRMS-ESI (*m/z*) calcd for $C_{10}H_{10}BrN_2$ $[M + H]^+$ 237.0022, found 237.0019.

3-Bromo-1-ethyl-5-methyl-1H-pyrazole (9k). Starting from crude **8k**/DCM solution (40.17 g solution, 8.72 wt% **8k** in DCM, 18.3 mmoles, 1.0 equiv), toluene (30 mL, 1.64 L/mole **8k**) and manganese dioxide (19.0 g, 219 mmoles, 12.0 equiv), with a manganese dioxide (3.20 g, 37.0 mmoles, 2.0 equiv) kicker charge after 26 h at 105-110 °C and an additional 18 h age, isolated 1.46 g of **9k** as a pale yellow oil in 42% yield after ISCO purification (80 g column, flow rate 60 mL/min, gradient 100% hexanes for 1 CV, then to 30% EtOAc over 3 CV, 30% EtOAc for 2 CV then to 100% EtOAc over 6 CV); R_f = 0.50 (2:1 hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 5.97 (s, 1 H), 4.01 (q, *J*= 7.5 Hz, 2 H), 2.23 (s, 3 H), 1.36 (t, *J*= 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 124.2, 107.6, 44.1, 15.2, 10.7; HRMS-ESI (*m/z*) calcd for $C_6H_{10}BrN_2$ $[M + H]^+$ 189.0022, found 189.0020.

1-Benzyl-3-bromo-5-methyl-1H-pyrazole (9l). Starting from crude **8l**/DCM solution (25.00 g solution, 10.77 wt% **8l** in DCM, 10.64 mmoles, 1.0 equiv), toluene (19 mL, 1.79 L/mole **8l**) and manganese dioxide (9.25 g, 106 mmoles, 10.0 equiv), with a manganese dioxide (1.85 g, 21.3 mmoles, 2.0 equiv) kicker after 28 h at 105-110 °C, and an additional 15 h age, isolated 1.32 g of **8l** as a pale yellow oil in 49% yield after ISCO purification (120 g column, flow rate 85 mL/min, gradient 100% hexanes for 2 CV, then to 10% EtOAc over 3 CV, 10% EtOAc for 4 CV then to 20% EtOAc over 3 CV); R_f = 0.28 (5:1 hex:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3 H), 7.13 (d, *J*= 5.0 Hz, 2 H), 6.09 (s, 1 H), 5.25 (s, 2 H), 2.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 136.1, 128.6, 127.6, 126.6, 124.7, 108.3, 53.2, 11.0; HRMS-ESI (*m/z*) calcd for $C_{11}H_{12}BrN_2$ $[M + H]^+$ 251.0178, found 251.0176.

General Procedure to Prepare 3-Chloropyrazoles. *3-Chloro-5-methyl-1-phenyl-1H-pyrazole (11a).* To a -12 °C mixture of **6e** (1.00 g, 5.68 mmoles, 1.00 equiv), dry tetraethylammonium chloride (282 mg, 1.70 mmoles, 0.30 equiv), 1,2-dichloroethane (6.00 mL, 6 L/kg) and triethylamine (712 µL, 5.11 mmoles, 0.90 equiv) was charged phosphorus oxychloride (686 µL, 7.38 mmoles, 1.30 equiv). The mixture was then aged at 60 °C for 3 h. The clear solution was then cooled to room temperature and quenched by addition into a 1.0 M, pH = 7 sodium phosphate buffer (10 mL, 10 L/kg). The layers were separated and the organic layer was washed with saturated aqueous brine (10 mL, 10 L/kg), dried over sodium sulfate, filtered and concentrated *in vacuo* to afford the intermediate chlorodihydropyrazole as a dark oil (1.2 g). Charged acetonitrile (10 mL, 10 L/kg) and manganese dioxide (7.40 g, 85.12 mmoles, 15.00 equiv) and aged black slurry at 60 °C for 8 h. The reaction mixture was then cooled to room temperature and filtered through a plug of Celite using acetonitrile to wash the cake (30 mL, 30 L/kg). The solution was then concentrated *in vacuo* to afford a dark red residue. The residue was purified by flash column chromatography over silica gel (0 to 20% ethyl acetate in hexanes gradient) to afford **11a** as an orange oil (900 mg, 82% overall yield, 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.38 (m, 5 H), 6.14 (d, *J* = 0.5 Hz, 1 H), 2.32 (d, *J* = 0.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 140.2, 139.0, 129.0, 128.0, 124.8, 106.0, 12.4; HRMS-ESI (*m/z*) calcd for $C_{10}H_{10}ClN_2$ $[M + H]^+$ 193.0527, found 193.0525.

3-Chloro-1-methyl-5-phenyl-1H-pyrazole (11b). Starting from **6i** (1.00 g, 5.68 mmoles, 1.00 equiv), dry tetraethylammonium chloride (282 mg, 1.70 mmoles, 0.30 equiv), dichloromethane (6.00 mL, 6 L/kg), triethylamine (712 µL, 5.11 mmoles, 0.90 equiv) and phosphorus oxychloride (686 µL, 7.38 mmoles, 1.30 equiv, added at -35 °C), with a 24 h age at 35 °C, followed by acetonitrile (10 mL, 10 L/kg) and manganese dioxide (7.40 g, 85.12 mmoles, 15.00 equiv) with a 17 h age at 60 °C, isolated 844 mg of **11b** as a yellow waxy solid in 77% yield (2-steps) after ISCO purification (0 to 20% ethyl acetate in hexanes gradient); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.38 (m, 5 H), 6.23 (s, 1 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 138.4, 129.5, 129.0, 128.8, 128.7, 104.8, 37.6; HRMS-ESI (*m/z*) calcd for $C_{10}H_{10}ClN_2$ $[M + H]^+$ 193.0527, found 193.0526.

3-Chloro-5-n-hexyl-1-methyl-1H-pyrazole (11c). Starting from **6o** (1.00 g, 5.43 mmoles, 1.00 equiv), dry tetraethylammonium chloride (275 mg, 1.63 mmoles, 0.30 equiv), dichloromethane (6.00 mL, 6 L/kg), triethylamine (688 µL, 4.88 mmoles, 0.90 equiv) and phosphorus oxychloride (664 µL, 7.05 mmoles, 1.30 equiv, added at -20 °C) with a 17 h age at 35 °C, followed by acetonitrile (10 mL, 10 L/kg) and manganese dioxide (4.72 g, 54.30 mmoles, 10.00 equiv) with a 4.5 h age at 60 °C, isolated 677 mg of **11c** as orange oil in 62% yield (2-steps) after ISCO purification (0 to 15% ethyl acetate in hexanes gradient, UV detector set to 207 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (s, 1 H), 3.72 (s, 3 H), 2.54 (app t, J = 7.7 Hz, 2 H), 1.65-1.56 (m, 2 H), 1.41-1.28 (m, 6 H), 0.90 (app t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 137.7, 103.2, 36.2, 31.4, 28.8, 28.1, 25.6, 22.5, 14.0; HRMS-ESI (*m/z*) calcd for $C_{10}H_{18}ClN_2$ $[M + H]^+$ 201.1153, found 201.1151.

3-Chloro-1-n-hexyl-5-trifluoromethyl-1H-pyrazole (11d). To a 0 °C mixture of **6p** (1.00 g, 4.20 mmoles, 1.00 equiv), dry tetraethylammonium chloride (213 mg, 1.26 mmoles, 0.30 equiv), 1,2-dichloroethane (6.00 mL, 6 L/kg) and triethylamine (532 µL, 3.78 mmoles, 0.90 equiv) was charged phosphorus oxychloride (509 µL, 5.46 mmoles, 1.30 equiv). The mixture was then aged at 60 °C for 3 h. The reaction mixture was then cooled to room temperature, quenched by addition into a 1.0 M, pH = 7 sodium phosphate buffer (20 mL, 20 L/kg) and the aqueous layer was extracted with dichloromethane (2 x 5 mL, 2 x 5 L/kg). The combined organic layers were dried over sodium sulfate, filtered, washed with dichloromethane (2 x 3 mL, 2 x 3 L/kg), cooled to 0 °C and charged with *N*-chlorosuccinimide (744 mg, 546 mmoles, 1.30 equiv). After 30 min, the mixture was warmed to room temperature, and after an additional 30 min, was poured into a saturated aqueous sodium thiosulfate. The aqueous layer was extracted with dichloromethane (2 x 10 mL, 2 x 10 L/kg), and the combined organic layers were dried over sodium sulfate, filtered, concentrated and purified by ISCO chromatography (0 to 5% ethyl acetate in hexanes gradient, UV detector set to 227 nm) to afford 598 mg **11d** as a light brown oil in 56% overall yield (2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1 H), 4.14 (app t, J = 7.4 Hz, 2 H), 1.88 (q, J = 7.3 Hz, 2 H), 1.39-1.28 (m, 6 H), 0.89 (app t, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.2 (q, J = 40.0 Hz), 119.2 (q, J = 269.3 Hz), 106.2 (q, J = 2.9 Hz), 51.8, 31.2, 30.0, 26.0, 22.4, 13.9; HRMS-ESI (*m/z*) calcd for $C_{10}H_{15}ClF_3N_2$ $[M + H]^+$ 255.0870, found 255.0866.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX.

Copies of ^{1}H and ^{13}C NMR spectra for all products

REFERENCES

(1) (a) Lamberth, C. *Heterocycles* **2007**, *71*, 1467. (b) Jeschke, P. The Unique Role of Halogen Substituents in the Design of Modern Crop Protection Compounds. In *Modern Crop Protection Compounds;* Kramer, W., Schirmer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 1189-1237. (c) Rouse, M.; Seefeld, M. A. WO 2010093885, 2010. (d) Le-Brun, A.; Thompson, F.; Tiraboschi, G.; Salvino, J. M.; Maillet, P. US 20050130989, 2005.

(2) Zhang, J.; Didierlaurent, S.; Fortin, M.; Lefrancois, D.; Uridat, E.; Vevert, J.P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2575.

(3) (a) For a review, see Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924 and references cited therein. (b) Bourrain, S.; Ridgill, M.; Collins, I. *Synlett* **2004**, 795.

(4) (a) Lahm, G. P.; Selby, T. P.; Stevenson, T. M. WO 2003015519, 2003. (b) Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; Freudenberger, D. C.; Flexner, L.; Bellin, C. A.; Dubas, C. M.; Smith, B. K.; Hughes, K. A.; Hollingshaus, G.; Clark, C. E.; Benner, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6274. (c) Lahm, G. P.; Cordova, D.; Barry, J. D. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 4127. (d) Huang, Z.; Tong, J.; Zhou, S.; Xiong, L.; Wang, H.; Zhao, Y. *J. Heterocyclic Chem.* **2016**, *53*, 1036. (e) Wu, J.; Song, B.-A.; Hu, D.-Y.; Yue, M.; Yang, S. *Pest Manag. Sci.*, **2012**, *68*, 801. (f) Wang, W.; Wang, L.-P.; Ning, B.-K.; Mao, M.-Z.; Xue, C.; Wang, H.-Y. *Phosphorous, Sulfur and Silicon* **2016**, *191*, 1362. (g) Hua, X.; Mao, W.; Fan, Z.; Ji, X.; Li, F.; Zong, G.; Song, H.; Li, J.; Zhou, L.; Zhou, L.; Liang, X.; Wang, G.; Chen, X. *Aust. J. Chem.* **2014**, *67*, 1491. (h) Berger, R. A.; Flexner, J. L. WO 2003024222, 2003. (i) Yang, Q.; Lorsbach, B.; Roth, G.; Niyaz, N. M.; Nissen, J.; Ross, R. Jr.; Whiteker, G.; Deamicis, C.; Gray, K.; Zhang, Y. WO 2015058028, 2015. (j) Nishioka, M.; Nakashita, H.; Suzuki, H.; Akiyama, S.; Yoshida, S.; Yamaguchi, I. *J. Pestic. Sci.* **2003**, *28,* 416. (k) Chupp, J. P. *J. Heterocyclic Chem*. **1994**, *31*, 1377. (l) Foti, F.; Grassi, G.; Risitano, F. *Tetrahedron Lett.* **1999**, *40*, 2605.

(5) (a) Badiger, S.; Behnke, D.; Betschart, C.; Chaudhari, V.; Chebrolu, M.; Costesta, S.; Hintermann, S.; Pandit, C. WO 2011076744, 2011. (b) Shigeaki, A.; Tomohisa, U.; Junichi, W. Jpn. Kokao Tokkyl Koho, 09316055, 09 Dec 1997.

(6) (a) Nokura, Y.; Ikegami, H.; Jachmann, M.; Tanaka, M. WO 2008126858, 2008. (b) Li, X.; Yang, Q.; Lorsbach, B. US 9085552, 21 July, 2015.

(7) Fox, R. J.; Markwalter, C. E.; Lawler, M.; Zhu, K.; Albrecht, J.; Payack, J.; Eastgate, M. D. *Org. Proc. Res. Dev.* **2017**, *21*, 754.

(8) For the preparation of the corresponding 3-iodo derivative, see Fitzgerald, M. A.; Soltani, O.; Wei, C.; Skliar, D.; Zheng, B.; Li, J.; Albrecht, J.; Schmidt, M.; Mahoney, M.; Fox, R. J.; Tran, K.; Zhu, K.; Eastgate, M. D. *J. Org. Chem.* **2015**, *80*, 6001.

(9) For the preparation of both **6e** and **6j**, it was optimal to use isopropyl versus methyl esters to minimize direct amidation.

(10) (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (b) Taylor, E.; Sobieray, D. M. *Tetrahedron* **1991**, *47*, 9599.

(11) Compound **6e** was also prepared via method B, but despite improved regioselectivity, isolated yield was lower.

(12) No reaction observed in DCM. Observed some product using CH_3CN at 80 °C, but significant decomposition was also observed.

(13) When starting from **6***HBr salts, Et_3N was added during bromination. Slightly different equivalents of Et_3N, reaction temperatures and aqueous workup protocols were found to be optimal for certain substrates. See Supporting Information for experimental details.

(14) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, 52, 2559.

(15) No over-bromination at C(4) was observed